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Not everything that can be counted counts, and not everything that counts can be counted.

Albert Einstein

Preface

This thesis was funded by the National Veterinary Institute, Technical University of Denmark, where I was enrolled at the Section of Epidemiology from December 2011 to July 2016, including three months research visit at the Department of Health Management, Prince Edward Island, Canada. I would like to thank all people helping me through. Thanks to all the farmers and practicing veterinarians showing me practical life and what is actually behind the excessive amounts of Danish register data. Thanks to the data providers (the Classification Authority, SEGES and DVFA). Without data, this thesis would not have been feasible!

Thanks to my supervisors Anette Boklund, Nils Toft, Claes Enøe, Helle Stege and Lasse Engbo Christiansen for sharing your knowledge, for input and discussions… Nils, thanks for your outspoken instant opinion clearing things out on what is actually important. Anette, thanks for your always open door, patience and endless feedback on papers with hints on how to move on. Although it wasn't planned from the beginning – the two of you made up quite a good main supervision team. It truly has been an educational journey which I wouldn't be without! Thanks to Claes, my main supervisor the first year, for giving me the chance to work on this project and to take ownership of it. And of course, thanks to Javier Sanchez and Henrik Stryhn which in my mind, are my Canadian supervisors and definitely the best hosts I could ever imagine. Thanks for your hospitality and engagement in my project.

And then, I would like to thank Nana Dupont, with whom I had the most VetStat-conversations, defeated the most data challenges and shared the most ideas and code during the last years. You were always there when needed. Thanks!

Thanks to the VetStat study group (Amanda Brinch Kruse, Camilla Birkegård, Leonardo de Knegt, Vibe Dalhoff Andersen, Gitte Blach Nielsen, Nana Dupont). Great discussions once we started. I would have wished you had been there at the time I started the PhD. Thanks to the advisory group (Anders Elvstrøm, Andreas Birch, Erik Jacobsen, Poul Bækbo, Elisabeth Okholm Nielsen) for your interest in the study, input and discussions. A special thanks to Erik (and his successor Laura Mie Jensen) for your readiness to talk about VetStat-issues whenever needed.

Former and present colleagues in the Epi-group at DTU Vet: Thanks for the laughs. You are awesome!

And last but not least, thanks to my husband, Chris, for the unconditional support and for holding our family together these last intensive months. Thanks to Frida and Iben for supplying life with joy! And to my mom for support in daily life whenever needed.

Mette — Frederiksberg, July 2016

Content

List of original publications

This thesis is a synthesis of the following manuscripts, which are referred to in Roman numerals in the text. All manuscripts are published in peer-reviewed journals with the exception of Manuscript I which is under preparation for submission to a peer-reviewed journal.

I. Lopes Antunes, A.C.*, **Fertner, M.***, Birkegård, A.C., Boklund, A., Halasa, T., Toft, N.
Swine databases: Evaluation of their quality and potential use for disease surveillance
In preparation

II. **Fertner, M.**, Sanchez, J., Boklund, A., Stryhn, H., Dupont, N., Toft, N.
Persistent spatial clusters of prescribed antimicrobials among Danish pig farms – a register-based study.
PLoS ONE 10(8), 2015

III. **Fertner, M.**, Boklund, A., Dupont, N., Toft, N.
Changes in group treatment procedures and its influence on the amount of administered antimicrobials.
Preventive Veterinary Medicine 126, 89-93, 2016

IV. **Fertner, M.**, Toft, N., Martin, H.L., Boklund, A.
A register-based study of antimicrobial usage in Danish veal calves and young bulls.
Preventive Veterinary Medicine 131, 41–47, 2016

V. **Fertner, M.**, Boklund, A., Dupont, N., Enøe, C., Stege, H., Toft, N.
Weaner production with low antimicrobial usage: A descriptive study.
Acta Vet. Scand. 57 (38), 2015

Author's contribution in co-authored publications:

I: Shared the first-authorship with A.C. Lopes Antunes. Assisted drafting the interview-guide and participated in conduction of the interviews on all databases which are assessed in the paper. Furthermore, responsible for (and drafted) parts of the manuscript dealing with VetStat, CHR and the Meat Inspection database.

II, III, IV: Conceived, designed and performed the studies, analyzed the results and further drafted the manuscripts.

V: Designed the interview-guide, contacted participating farmers and veterinarians, carried out the on-farm interviews, analyzed the results and drafted the manuscript.

Summary

Prudent use of antimicrobials in production animals is an ongoing theme of discussion on the political scene, caused by the rise in antimicrobial resistance. For decades, antimicrobials have been used in production animals for therapeutic, metaphylactic and prophylactic treatments as well as for growth promotion. In Denmark, around 30 million pigs and around 200,000 veal calves are produced annually. The two production systems are similar in the way that they fatten up young animals for slaughter. Young age and a high turn-over of animals increases the risk of disease and antimicrobial use. In Denmark, pigs consume the majority of antimicrobials for veterinary use (76%), and have therefore been the focus of political attention in the reduction of antimicrobial use. Since the 1990s, several political initiatives have been implemented to reduce antimicrobial use in production animals, including the Danish Veterinary Medicines Statistics Program (VetStat) in 2000.

In addition to VetStat, Denmark holds a number of other databases for pigs and cattle. These databases contain large amounts of data, which are increasingly being used for research purposes due to their availability.

It is important to elucidate factors that influence antimicrobial use in the herd when striving towards minimum usage without compromising animal health. Based on data in the registers, this thesis is split into five subsections, each with its own objective:

Objective 1: Present a selected set of Danish pig registers and evaluate data quality

Objective 2: Describe antimicrobial use over time and space

Objective 3: Assess the effect of changed group treatment procedure on the antimicrobial use at the herd-level

Objective 4: Study the effect of animal movements on the antimicrobial use at the herd-level

Objective 5: Describe factors unavailable in the registers that may impact antimicrobial use

Based on guidelines from the European Centre for Disease Prevention and Control (ECDC) monitoring data quality and surveillance systems, we evaluated seven Danish pig databases: The Central Husbandry Register (CHR), the Swine Movement Database (SMD), VetStat, data from two diagnostic laboratories – the National Veterinary Institute – Technical University of Denmark (DTU Vet) – and the Pig Research Center-SEGES (VSP)), the Specific Pathogen Free System (SPF System), and the meat inspection database. In general, data quality seemed to improve when economic or legislative implications were linked to the data (Manuscript I).

A repeated cluster analysis was performed with antimicrobial use as a continuous outcome to test for the presence of persistent clusters of pig herds with high-antimicrobial use throughout 2012-13. Four analyses were performed: Three univariate analyses (on antimicrobial use in weaners, finishers and sows) and one multivariate analysis, combining antimicrobial use for all three age groups into one single analysis. The univariate analyses, revealed two persistent clusters for finishers and one for sows, while we did not find any for weaners. The multivariate analysis resulted in three persistent clusters, which coincided with areas of high farm density and was partially explained by production type, farm type and farm size (Manuscript II).

Based on registrations of purchased drugs in VetStat, we identified pig herds which had changed their group treatment procedure completely from feed to water administration. We compared their total antimicrobial use one year prior to one year after the shift, and found that the use had increased significantly, most likely due to the treatment of more pigs (Manuscript III). These results elucidate the importance of group treatment and application forms.

Studying the effect of animal movements on antimicrobial use, we investigated veal herds, for which animal movements are registered at the animal-level. This enabled us to study whether the following factors affected the antimicrobial use at the herd-level, namely the effect of number of suppliers, number of calves purchased, the frequency of purchase, the average age at introduction, the average time in the herd and vaccination. A multivariable regression analysis revealed the number of calves purchased to be the only factor significantly associated with the amount of used antimicrobials (Manuscript IV).

For the last study, we hypothesized well-managed weaner productions, with similar production results, to have a set of common key-factors which could be identified and used for general recommendations. Hence, we identified 11 weaner producers, which according to the registers were alike; in the good-league in terms of mortality, daily weight gain and antimicrobial use. However, on-farm visits and interviews revealed wide variation between farmers; with many having a specific point of focus, e.g. feeding, refurbishment of facilities, medication method, and attentiveness in the shed. These results stress the importance of the specific farmer and calls for further studies on farmer-characteristics (Manuscript V).

This thesis elucidated the potential application and limitations of using register data for research purposes. We identified a number of factors in the registers that may influence the amount of antimicrobials used at farm-level, namely geographical region (Manuscript II), treatment procedure (Manuscript III) and patterns of purchase (Manuscript IV).

Sammendrag

Ansvarlig brug af antibiotika til produktionsdyr er et tilbagevendende emne på den politiske dagsorden, grundet udviklingen af resistente bakterier. I årtier er antibiotika til produktionsdyr blevet brugt til terapeutiske, metafylaktiske, profylaktiske behandlinger og som vækstfremmere. I Danmark produceres der årligt omkring 30 millioner grise og 200.000 slagtekalve. Produktionstyperne har det til fælles at opfede unge dyr til slagt. Modtageligheden for sygdom er større blandt unge dyr, hvilket sammen med den høje udskiftningsrate øger risikoen for brug af antibiotika. I Danmark bruges hovedparten af den veterinære antibiotika til grise (76%), som derved har været det politiske fokus i reduktionen af antibiotika. Siden 1990erne er der således blevet gennemført adskillige politiske initiativer til at reducere brug af antibiotika i husdyrproduktionen, inklusive indførelsen af den danske database over veterinære lægemidler (VetStat) i år 2000.

Udover VetStat er der I Danmark talrige andre databaser for grise og kvæg. Databaserne indeholder adskillige mængder data, der på grund af tilgængeligheden af data bliver brugt i stigende omfang til forskningsformål.

For at kunne minimere antibiotikaforbruget uden at være på bekostning af dyrenes sundhed, er det nødvendigt at klarlægge faktorer, som påvirker antibiotikaforbruget. Alle undersøgelser i dette ph.d. studium er baseret på register data, og er inddelt i fem delemner, repræsenteret i form af følgende formål:

Formål 1: Præsentere et udvalgt antal af danske databaser til grise og evaluere data kvaliteten

Formål 2: Beskrive antibiotikaforbruget i tid og sted

Formål 3: Vurdere om effekten af ændringer i procedurer for flokbehandling kan influere på antibiotikaforbruget

Formål 4: Undersøge effekten af flyttemønstre på antibiotikaforbruget

Formål 5: Beskrive faktorer, som ikke er tilgængelige i registrene, men som stadig har en effekt på antibiotikaforbruget

Baseret på retningslinjer fra det Europæiske Center for Sygdomsforebyggelse og -kontrol (ECDC), der har til formål at overvåge data kvalitet og overvågningssystemer, evaluerede vi syv danske databaser omhandlende grise: det Centrale Husdyr Register (CHR), Svineflyttedatabasen (SMD), VetStat, diagnostisk data fra to laboratorier (på Veterinærinstituttet og Laboratoriet for Svinesygdomme i Kjellerup (SEGES)), Specifik Patogen Fri (SPF) og registreringer fra kødkontrollen. Generelt set, forbedredes datakvaliteten idet data relaterede til økonomiske eller lovmæssige forhold (Manuskript I).

Til formål 2, lavede vi en cluster analyse med antibiotikaforbrug som kontinuert outcome. Vi gentog hver analyse for fire tidsenheder for at identificere geografiske områder, hvor antibiotikaforbruget forblev vedvarende højt i løbet af 2012-13. Denne fremgangsmåde gentog vi af fire omgange; som tre univariate analyser (antibiotikaforbrug for henholdsvis klimagrise, slagtegrise og søer) og en multivariat analyse, hvori antibiotikaforbruget for alle tre aldersgrupper blev evalueret på en gang. De univariate analyser resulterede i to persisterende cluster for slagtesvin, et for søer og ingen for klimagrise. Den multivariate analyse resulterede i tre persisterende clustre i antibiotikaforbruget. Disse multivariate clustre fandtes i områder med høj besætningstæthed, og kunne delvist forklares af type af produktion, besætningstype og besætningsstørrelse (Manuskript II).

På baggrund af registreringer om salg af lægemidler i VetStat, identificerede vi besætninger som fuldstændigt havde ændret flokmedicinering fra foder- til vand-administration. Besætningernes antibiotikaforbrug steg signifikant, når man sammenlignede deres antibiotikaforbrug året inden skift med året efter skift af medicineringsmetode, hvilket formentlig skyldes behandling af flere grise (Manuskript III). Disse resultater understreger vigtigheden af administrationsformer ved flokmedicinering.

Undersøgelse af effekten af flytninger valgte vi at lave på slagtekalve, idet flytninger for kvæg registreres på enkeltdyrsniveau. På den måde fik vi muligheden for at undersøge faktorer såsom antal leverandører, antal indkøbte kalve, hyppigheden af indkøb, gennemsnitlig indsættelsesalder, gennemsnitlig længde dyrene er på besætningen og vaccine. Vi lavede en multivariabel regressions analyse, der angav antallet af indsatte kalve til at have en positiv sammenhæng med brugen af antibiotika på besætningen, hvilket understreger vigtigheden af ekstern smittebeskyttelse (Manuskript IV).

I den sidste undersøgelse var vores hypotese at veldrevne klimagrise-besætninger, med ens produktionsresultater, har et sæt nøglefaktorer til fælles i managementet, som ville kunne bruges i anbefalinger til andre klimagriseproducenter. Vi fandt 11 klimagrise producenter, som ifølge registrene havde ens resultater; i den bedre halvdel i forhold til dødelighed, daglig tilvækst og antibiotikaforbrug. Imidlertid fandt vi store forskelle i landmændenes management. Flere havde et bestemt fokus-område som for eksempel fodring, investering i bygningerne, medicineringsstrategi eller almen årvågenhed. Disse resultater indikerer vigtigheden af den enkelte besætningsejer og behovet for studier af landmands-typer relateret til effekt på antibiotikaforbruget (Manuskript V).

Denne afhandling klarlagde anvendelsesmuligheder og begrænsninger for brug af register-data i forskning. Baseret på register-data identificerede vi et antal faktorer, som havde betydning for antibiotikaforbruget på besætningsniveau, nemlig geografisk område (Manuskript II), medicineringsmetode (Manuskript III) og flyttemønstre (Manuskript IV).

Abbreviations

ADD: Animal Daily Doses

ATC: Anatomical Therapeutic Chemical Classification System

CHR: Central Husbandry Register

DVFA: Danish Veterinary and Food Administration

EU: The European Union

LA-MRSA: Livestock Associated methicillin-resistant *Staphylococcus aureus*

NSC: Non-specific colitis

PCV2: Porcine Circovirus type 2

PRRS: Porcine Reproductive and Respiratory Syndrome

PMWS: Post Weaning Multisystemic Wasting Syndrome

SPF: Specific Pathogen Free system

VAC: Veterinary health Advisory Contract

VetStat: The Danish Veterinary Medicines Statistics Program

WHO: The World Health Organization

1. Introduction

1.1 Background

The World Health Organization (WHO) has declared antimicrobial resistance one of the greatest threats to human health in the 21st century (Nordberg et al., 2013). In the European Union, around 25,000 people die annually from infections with multidrug-resistant bacteria. This corresponds to an annual cost of 1.5 billion euros for healthcare and loss of productivity (ECDC and EMEA, 2009). In 1969, the Swann Report was the first to address the possible link between veterinary antimicrobial use and bacterial resistance in human beings (Swann et al., 1969). Nearly 50 years later, the extent to which antimicrobial use in veterinary medicine contributes to the emergence of resistant human pathogenic bacteria is still debated. Nevertheless, it has been shown that antimicrobial use does lead to the selection of resistant bacteria and that animals constitute a potential reservoir of bacterial resistance genes (Martel et al., 2001; Schwarz et al., 2001; Catry et al., 2003). A clear association between the amount of veterinary antimicrobials used and the level of antimicrobial-resistant bacteria isolated from animals has been demonstrated (Chantziaras et al., 2014). Veterinary antimicrobial use is expected to increase by 67% worldwide over the next 15 years. This increase is mainly due to a rising demand for livestock products in middle-income countries. By the year 2030, countries like Brazil, Russia, India, China and South Africa are expected to have increased their use of veterinary antimicrobials by 99% (Van Boeckel et al., 2015).

1.2 Historical outline of antimicrobial use in production animals from a Danish perspective

In the 1950s, the first antimicrobials were introduced to the veterinary field with a subsequent major improvement in terms of health, welfare and productivity among livestock. Soon after, the growth-enhancing effect of antimicrobials added in sub-therapeutic levels to feed was observed, and the use of growth-promoters became widespread across the world (Martel et al., 2001). The Swann Committee was established following concern that the use of antimicrobials in animal production could lead to the emergence of resistant bacteria for both humans and animals. Based on their recommendations (Swann et al., 1969), it was decided that only antimicrobials with little or no therapeutic application in human or veterinary medicine should be used as growth promoters (European Council, 1970). Decades later, it was discovered that antimicrobials used in growth promotion could cause cross-resistance to antimicrobials used in human medicine, despite different active compounds (McDonald et al., 1997).

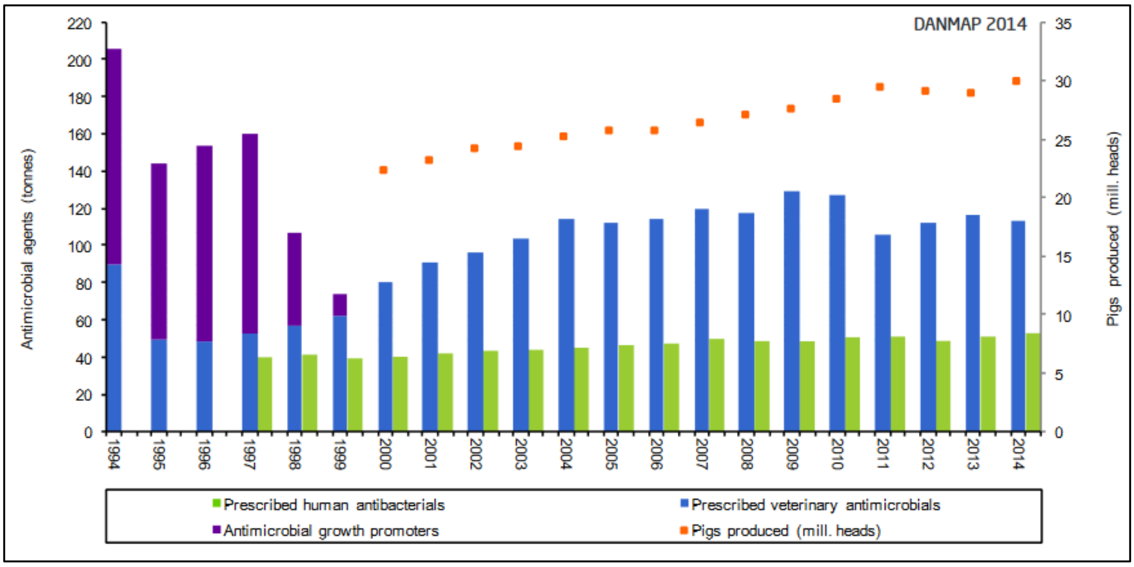

Figure 1: Prescribed antimicrobial agents for humans and for animals compared to the number of pigs produced in Denmark. *Antimicrobials are categorized as either therapeutic or antimicrobial growth promoters (DANMAP, 2015).*

The European Union banned the use of growth promoters from 1st of January 2006 (European Parliament, 2003). Prior to that, the Danish poultry and swine industries had voluntarily phased out growth promoters for broilers in February 1998, for finishers in April 1998 and for all pigs January 2000 (Emborg et al., 2001; Aarestrup et al., 2010). In combination with a national legislation prohibiting veterinary profit from the sale of antimicrobials in 1994, the ban on growth promoters decreased the total use of antimicrobials in Denmark substantially during the late 1990s (Figure 1) (Aarestrup et al., 2010; DANMAP, 2015). In 1995, Veterinary health Advisory Contracts (VAC) were introduced. The idea behind VAC was to focus on preventive measures and to compensate the veterinary loss of income from the antimicrobials. Danish cattle and pig farms with a VAC have a contract with a veterinary practice that will perform regular health visits on the farm (Anonymous, 1995a). Accordingly, farmers are allowed to administrate prescribed antimicrobials themselves, based on instructions from a veterinarian (Anonymous, 1995b).

In 1998, Copenhagen hosted an EU conference named the Microbial Threat, which dealt with the emerging antimicrobial resistance. This resulted in The Copenhagen Recommendations, which included each country implementing a national system to collect data on antimicrobial use. In Denmark this resulted in the foundation of the Danish Veterinary Medicines Statistics Program (VetStat) in 2000 (Stege et al., 2003). VetStat is the national Danish database, in which the purchase of all veterinary prescription drugs is recorded (Stege et al., 2003). Using this database to strive towards a reduction in antimicrobial use, Denmark was the first country in the world to implement national thresholds on the maximum amount of antimicrobials permitted in pig and cattle farms, as laid down in the so-called "Yellow Card" directive (Anonymous, 2010a).

The Yellow Card thresholds for pigs were initially set at twice the average usage for each of the three age groups, thus targeting 5% of the farms with the highest use of antimicrobials (DANMAP, 2011; Jensen et al., 2014). From 2009 to 2011, the total amount of antimicrobials prescribed for pigs reduced by 25% (distributed as 31% in sows/piglets, 34% in weaners and 19% in finishers), which may be due to fewer systematic metaphylactic treatments in weaners and finishers (Jensen et al., 2014). There have since been two further reductions in the threshold values. Farms exceeding the threshold are subject to increased attention at the expense of the farmer. This may include: an increase in the number of VAC (Anonymous, 2016a), supplementary veterinary advice from a veterinarian approved by DVFA, unannounced visits from DFVA, restrictions on group medication and reduction of the occupancy rate (Anonymous, 2014a).

Today, antimicrobial treatment of production animals is only allowed when animals are clinically sick or are in a well-defined incubation period (Anonymous, 2015). In September 2013, differentiated taxes on antimicrobial substances were introduced to lower the use of broad-spectrum antimicrobials in favour of narrow-spectrum antimicrobials and vaccines (DANMAP, 2015). In addition, prescription of group treatment requires yearly positive laboratory diagnosis, and can be prescribed for a maximum period of 35 days, while antimicrobials administered for individual treatments can be prescribed for a maximum period of 63 days (Anonymous, 2014b; Anonymous, 2014c).

Since 1996, the DFVA have developed and maintained detailed treatment guidelines for veterinarians, in order to support the correct choice of antimicrobials for common clinical indications (Aarestrup et al., 2010; DVFA, 2015). Following the Yellow Card, the industry also developed a good practice manual for farmers on working with antimicrobials. This manual describes management procedures intended to prevent diseases in pigs, as well as the correct procedures for the administration and dosing of antimicrobials (SEGES, 2011).

1.3 Production animals and clinical indications for treatment

In terms of economy, the value of Danish animal production is made up of pork (22 billion DKK), milk (15 billion DKK), fur animals (8 billion DKK), veal- and beef meat (3 billion DKK), poultry meat (2 billion DKK) and eggs (0.7 billion DKK) (Danish Agriculture & Food Council, 2015a). Denmark is one of the largest exporters of pork, which constitutes 5% of the total national export. In 2014, 30 million pigs were produced, of which 19 million were slaughtered in Denmark and 11 million were exported. Similarly, 0.56 million cattle were slaughtered, of which approximately 50% were cows and 50% bulls and heifers (Danish Agriculture & Food Council, 2015b). Census data from summer 2014, estimate 12.5 million pigs (Danish Agriculture and Food Council, 2015c) and 1.6 million cattle (Danish Agriculture & Food Council, 2015b) to be present in Denmark at the time.

In terms of live biomass, cattle and pigs make up an equal percentage of the Danish animal population (Figure 2). However, pigs consume the majority of antimicrobials (76%). This can be explained by the high turnover in the pig production and the larger numbers of pigs (as described above) resulting in a proportionally younger and larger population than cattle. This difference may explain the higher antimicrobial use for pigs, since young animals are at higher risk of disease (DANMAP, 2015).

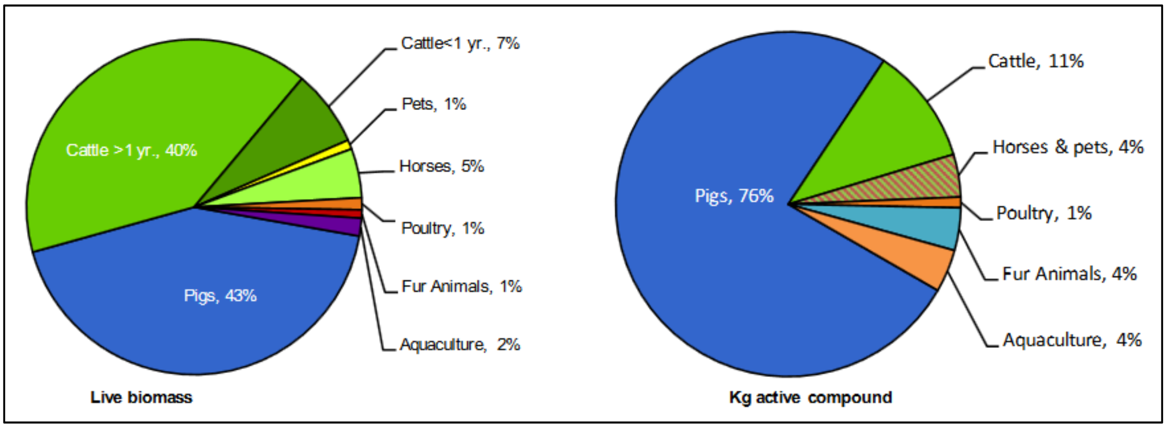

Figure 2: Live biomass (mill. kg) and antimicrobial consumption (kg) in main animal species, Denmark 2014. *Live biomass is calculated based on census data (DANMAP, 2015).*

For pigs, the vast majority of antimicrobial treatments are given to weaners, followed by finishers and sows/piglets (Jensen et al., 2014;DANMAP, 2015). For weaners and finishers, antimicrobials are primarily prescribed for gastrointestinal disorders (75% and 60%), respiratory disorders (16% and 20%) and musculoskeletal/CNS/dermal disorders (8% and 18%) (Jensen et al., 2014). The most common gastrointestinal pathogens in Danish weaners and finishers include *Lawsonia intracellularis, Brachyspira pilosicoli, Eschericia coli* and Porcine Circovirus type 2 (PCV2) (Pedersen et al., 2012). However, diarrhea may also be of non-infectious origin, e.g. non-specific colitis (NSC), which is non-respondent to antimicrobial treatment (Pedersen et al., 2012). *E. coli* infections mainly occur directly after weaning. An increase in age and weight at weaning and zinc oxide supplements in the feed has reduced *E. coli* infections (Heo et al., 2010; Pedersen, 2012; DANMAP, 2015). However, *E. coli* is still seen along with *L. intracellularis* and *B. pilosiloci* in weaned pigs, usually in infections where more pathogens are involved (Pedersen et al., 2014). Treatment with pleuromutilins is recommended for both *L. intracellularis* and *B. pilosicoli,* while colistin is used for diarrhea associated with *E. coli* (DVFA, 2015).

Prevalent respiratory pathogens in finishers include *Actinobacillus pleuropneumoniae* serotype 2, 6, 12, *Mycoplasma hyopneumoniae,* Influenza virus, Porcine Circovirus type 2 and Porcine Reproductive and Respiratory Syndrome virus (Afonso et al., 2006). The antimicrobial treatment is not directed at the viral pathogens themselves, but rather at any possible bacterial infection following immunosuppression. Vaccination against *M. hyopneumoniae* and PCV2 is widespread in Danish pig production, where 15 mill and 14.6 mill doses were sold in 2014, respectively. Substantially fewer vaccines were sold for *A. pleuropneumoniae* (4.8 mill doses) and influenza virus (1.4 mill doses) (DANMAP, 2015). The primary respiratory pathogen treated in Danish finishers is *A. pleuropneumoniae*, which may also affect other age groups and can be treated with penicillin, tetracycline, sulphonamide-trimethoprim, amphenicol and pleuromutilin (Taylor, 2006; DVFA, 2015). In addition to *A. pleuropneumoniae* and the above-mentioned viruses, respiratory disorders in weaners may be induced by *Bordetella bronchiseptica, Pasteurella multocida* and *Streptococcus suis* (Afonso et al., 2006). All may be treated with penicillin or pleuromutilin (DVFA, 2015).

Indications for antimicrobial prescriptions in sows/piglets are primarily limb/joint/CNS/skin disorders, followed by urogenital, gastrointestinal, respiratory and udder disorders (Jensen et al., 2014). For sows, the category of limb/joint/CNS/skin disorders primarily covers arthritis and hoof infections, while urogenital and udder disorders primarily cover mastitis-metritis-agalactia (Anders Elvstrøm, personal communication 2016). The etiology of mastitis-metritis-agalactia is unclear. *E. coli* and *Klebsiella* spp. are often involved, indicating treatment with broad-spectrum antimicrobials (Radostits et al., 2000; Taylor, 2006). Recommended treatment includes penicillin or pleuromutilin (DVFA, 2015). Arthritis in sows may be caused by *Erysipelothrix rhusiopathiae, Streptococcus* spp. and *Haemophilus parasuis*, while *Mycoplasma hyosynoviae* is primarily seen in gilts (Afonso et al., 2006). Typically, Danish sows are vaccinated against *Erysipelothrix rhusiopathiae* (2 mill doses in 2013), while the vaccination rate against *Haemophilus parasuis* has increased since 2008 to reach a similar level (Kruse, A.B., personal communication 2016). Streptococcal arthritis may be treated with penicillin or pleuromutilins (DVFA, 2015).

For antimicrobials registered for sows/piglets, piglets are responsible for the majority of treatments for gastrointestinal and respiratory disorders. Diarrhea in piglets is typically caused by *E. coli* or *Clostridium perfringens* type A or C and rotavirus (Radostits et al., 2000). Furthermore, diarrhea may be unresponsive to antimicrobials where no known pathogens can be identified, such as Neonatal Porcine Diarrhea (Kongsted et al., 2013). Vaccination of sows against both *Cl. perfringens* type C and *E. coli* is widespread, preventing neonatal diarrhea in the piglets (DANMAP, 2015). Penicillin or tiamulin may be used in the treatment of *Cl. perfringens* (DVFA, 2015). In addition to the previously mentioned *B. bronchoseptica, P. multocida, H. parasuis* and *A. plauropneumoniae, Mycoplasma hyorhinis* may also be involved in respiratory disorders of piglets (Afonso et al., 2006).

Veal calf production is a minor production in Denmark, with approximately 200,000 veal calves (<366 days of age) and young stock (>365 days of age) slaughtered in 2014 (Danish Agriculture & Food Council, 2015b). Veal calf production has certain similarities with slaughter pig production, where young animals are kept in groups of a similar age and fattened for slaughter. In 2014, 15% of the antimicrobials purchased for bovine use were used in calves (<366 days of age), calculated as kg active compound (DANMAP, 2015). Around half of these were used for veal calves and young stock (Fertner et al., in press).

Respiratory disease is the main indication for antimicrobial treatment in Swiss and Belgian veal calves (Pardon et al., 2012b; Lava et al., 2016a), followed by arrival prophylaxis (13%) and diarrhea (12%) in Belgian veal calves (Pardon et al., 2012a). In Denmark, no studies have as yet been carried out on indications for antimicrobial use in veal calves. A 30-year-old study showed respiratory disease and enteritis to be the two most common clinical diseases within the first 8 weeks after arrival in seven specialized veal calf herds (Madsen, 1984). Pathogens isolated from severe outbreaks of calf pneumonia in Denmark include bovine respiratory syncytial virus, *Pasteurella multocida*, *Histophilus somnus*, *Mannheimia haemolytica*, *Arcanobacterium pyogenes* (Tegtmeier et al., 1999), Bovine coronavirus (Liu et al., 2006) and most recently *Mycoplasma bovis* (Nielsen, 2016).

1.4 Administration of antimicrobials

Four purposes of administering antimicrobials for production animals exist: therapeutic, metaphylactic, prophylactic treatments, and as growth promoters (Schwarz et al., 2001). Only the first two applications are currently approved for Danish production animals (Anonymous, 2015). Growth promotion has been discussed in the previous chapter and will not be described any further.

Therapeutic treatment is the treatment of clinically sick animals. Production animals are often kept in large groups, thus increasing the transmission of infectious diseases. In cases where infection is expected to spread between individual animals, metaphylactic treatment becomes applicable. **Metaphylactic treatment** is the treatment of clinically healthy animals that are expected to be in a pre-defined incubation period, usually because they are held in groups with clinically sick animals. Early medication of such animals may prohibit the development of adverse clinical disease and thus reduce production losses. **Prophylactic treatment** is the treatment of clinically healthy animals to prevent disease at a critical point of the production period, e.g. at weaning, after transportation or mixture of new animals (Schwarz et al., 2001; Aarestrup, 2005).

In Denmark, oral group medication is most commonly used for pigs. During the last decade, the route of administration of group medication has changed from feed to water (Figure 3). This change is most likely due to the phasing out of growth promoters at the end of the 1990s, which resulted in a drastic reduction of pre-medicated feedstuff sold by the feed mills (Dupont, 2016). Preparation of medicated feed has therefore become more labor-intensive for the farmer, since it typically involves them mixing an antimicrobial premix into the feed (SEGES, 2011). In addition, farmers and veterinarians have increased the awareness of the advantages of antimicrobials added to water. Diseased pigs may become anorectic, while their water consumption stays unchanged. Additionally, antimicrobials added to water mix homogenously. For these reasons, diseased pigs are more likely to absorb the intended dose of medication if it is administered water compared to feed.

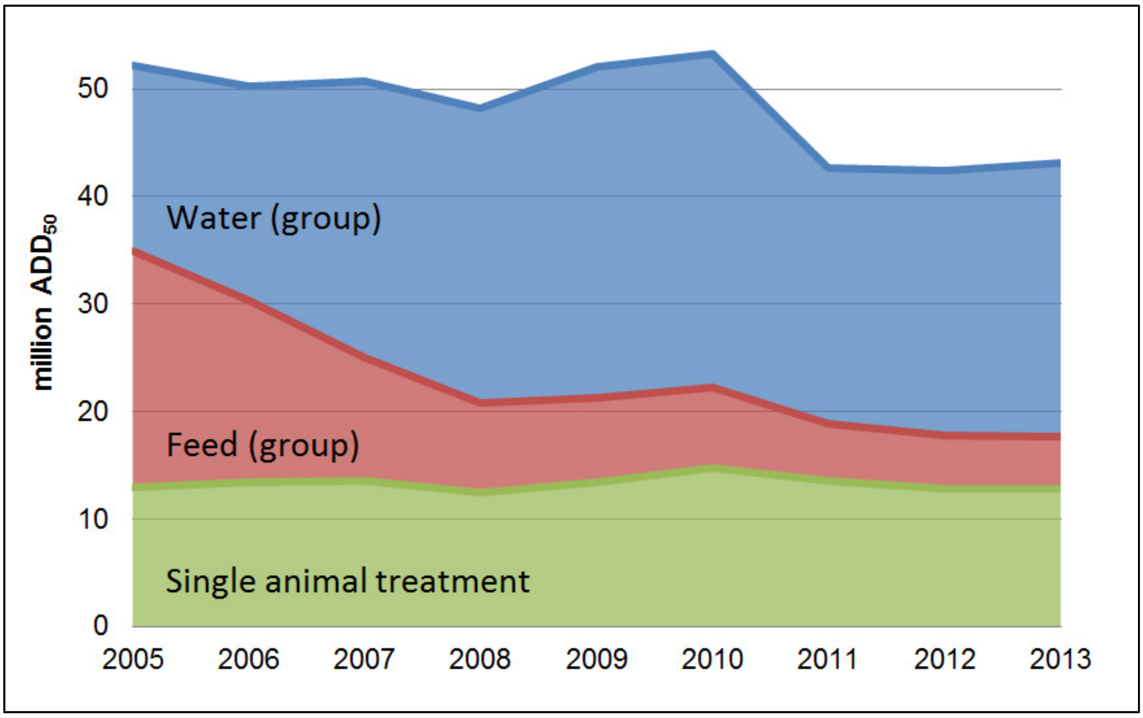

Figure 3: The cumulative amount of antimicrobials registered for all Danish finishers during 2005-2013, by administration route. *Antimicrobials are quantified as Animal Daily Doses, ADD_{50} for single animal treatments (green) and group treatments. Group treatments are characterized as water (blue) or feed (red) administrations (Fertner et al., 2015).*

As seen in Figure 4A, antimicrobial group treatment is mostly used in weaners, followed by finishers, while sows are mainly treated individually. Gastrointestinal and respiratory disorders are the two primary reasons for group medication in finishers (Figure 4B).

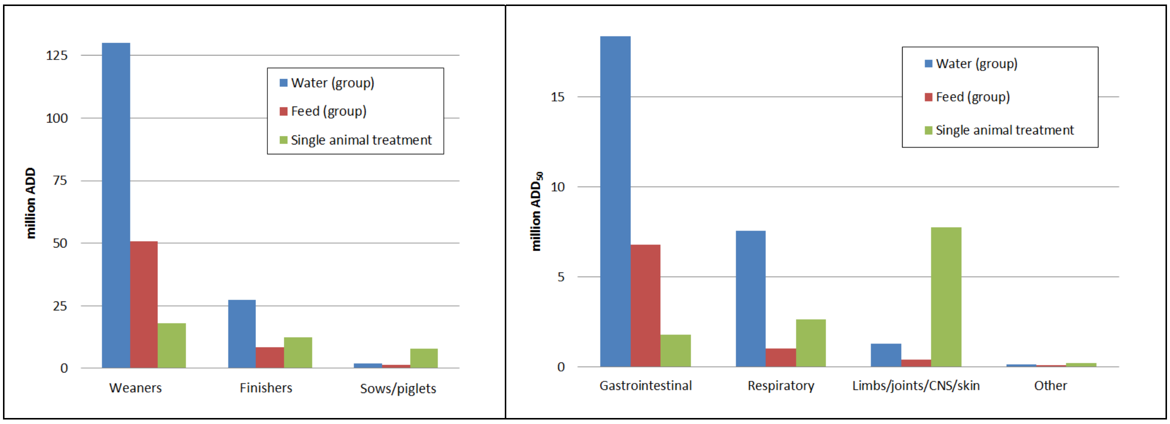

Figure 4A (left): Total amount of antimicrobials used for weaners, finishers and sows/piglets during 2008, by administration route. *Antimicrobials are quantified as Animal Daily Doses; ADD_{15}, ADD_{50} and ADD_{200} for weaners, finishers and sows/piglets, respectively.* ***4B (right): Antimicrobials used for finishers in 2008, by indication and administration route.*** *Antimicrobials are quantified as Animal Daily Doses, ADD_{50}. The majority of antimicrobial group treatments for finishers were for gastrointestinal and respiratory disorders, while single animal treatments were mainly used for limb/joint/CNS/skin disorders. "Other" disorders include prescriptions registered for reproduction/urogenital, udder or generalized disorders, or indications that were recorded as N/A.*

1.5 Registers

Denmark has a long tradition of transparent national registers in human (Sorensen and Schulze, 1996) as well as veterinary (Houe et al., 2011) medicine. Data from registers are increasingly being used in veterinary research (Vigre et al., 2010; Hybschmann et al., 2011; Alban et al., 2013; Jensen et al., 2014). Using register data allows for large amounts of secondary data to be accessed. In a research framework, primary data are defined as data collected for a specific purpose, while secondary data are defined as data that have not been collected for a specific research purpose. Instead, secondary data may have been collected for purposes such as administration, control or surveillance. The benefits of secondary data are that costly and time-consuming data collection involving questionnaires and herd visits can be avoided, and that such data may cover a large proportion of the population, which limits selection biases. However, as data are collected for other purposes, the researcher has no influence on the selection process of secondary data, and may often be unaware of the collection process and data quality. Therefore, it is absolutely necessary to have a thorough knowledge of the data in order to identify the limitations and precautions that need to be taken when handling and analyzing data (Sorensen et al., 1996; Emanuelson and Egenvall, 2014).

In the Danish livestock sector, both public and industry-owned registers exist. For pigs, the public databases include VetStat and the Central Husbandry Register (CHR) - including the Swine Movement Database. The CHR holds information on farm demographics such as geographical location, the number of animals according to species and age groups, and a farm identification number. All other databases relate to the farm identification number as stated in CHR. The farmer is responsible for recording information in both the CHR and the Swine Movement Database. Together, both registers allow the traceability of all pigs. VetStat records detailed information on the purchase of prescription-only drugs at farm level. The veterinarian sends the prescriptions to either the feed-mill (medicated feed) or pharmacy, from which the farmer buys the product. The product is not registered in VetStat until the time of purchase. Regarding drugs administered by a veterinarian (e.g. in relation to a farm visit), the amount of administered drug is registered directly in VetStat by the veterinarian (<2% of the registrations). Industry-based databases include the Specific Pathogen Free (SPF) register and the laboratory registers. The purpose of the SPF register is the transparency of the health status of herds in the SPF system. In addition, participating farms need to live up to a certain level of biosecurity. The SPF register extracts data on farm demographics from the CHR and adds diagnostic test results from the laboratory registers.

In contrast to pigs, data on Danish cattle are gathered in one single, extensive database (the Danish Cattle database), which is owned by the farmers and administered by SEGES Dairy and Beef Research Centre. The Danish Cattle database dates back more than 50 years, where the original purpose was to monitor milk quality. Since then, the purpose of the database has expanded to also include data on the movement of animals, milk production, reproduction, health, feeding and slaughter remarks. The registrations are therefore performed by a variety of sources, for example, the farmer, veterinarian, hoof trimmer, laboratories, dairies and abattoirs. Some recordings are mandatory, while others are voluntary. Recordings on movements are mandatory and include both movements of animals between farms, calving, culling and slaughter. Movements are registered at animal level and are registered twice (by the farmer receiving and delivering) to insure data quality (Nielsen, 2012; Frandsen, 2013).

2. Aim of the thesis

Antimicrobials are used to treat diseased animals. However, high antimicrobial use does not necessarily correspond to a high level of disease – and opposite. Some farmers may overlook diseased animals, while others are better to detect clinical diseased animals. The perception of a diseased animal, the threshold for initiating treatment as well as the method of administrating treatment may differ between farmers. As such, many factors can influence the amount of antimicrobials used on-farm.

Based on data in the registers, the aim of this thesis was to investigate health- and management-related factors associated with antimicrobial use on-farm, exemplified in the study of Danish pig and veal calf farms.

The objectives and hypotheses of the thesis were as follows:

Presentation of registers

1) To present Danish pig registers and their pitfalls

   Hypothesis: Databases constitute a valuable source of large amounts of secondary data. However, limitations exist in the application of the data in research, depending on the setup of the database and combination with other databases.

Combination of registers to identify factors in the management driving antimicrobial use at herd-level

2) To describe how antimicrobial use is distributed in time and space

   Hypothesis: We hypothesized that the use of antimicrobials remained significantly higher in certain areas over time, due to the stability of factors such as farm density, veterinary affiliation and treatment practices.

3) To study whether changed group-treatment procedures influenced the amount of antimicrobials used

   Hypothesis: We suspected a change in group-treatment procedures (from feed to water administration) would increase the total use of antimicrobials, as more pigs would be treated.

4) To describe the influence of animal movements on the use of antimicrobials

   Hypothesis: We suspected that the number of introduced animals, suppliers and the frequency of purchase would be positively correlated with the amount of antimicrobials used, while the age at entrance and the time in the herd would be negatively correlated with the amount of antimicrobials used.

Factors unavailable in the registers

5) To describe the factors that influence antimicrobial use, which are not available in the registers

   Hypothesis: We hypothesized that well-managed weaner producers would have a common set of management practices. Identification of such practices could be used in the development of guidelines for optimizing antimicrobial use without compromising animal health.

3. Materials and definitions

3.1 Quantification of antimicrobials at herd-level

Antimicrobials may be quantified in several ways (Chauvin et al., 2001). The simplest way of quantifying antimicrobials based on purchase records is in total kilogram of active substance. However, the potency of antimicrobials varies between active substances, which means that the same amount of two different drugs can be used to treat a different number of animals. Variation in the quantity of active substance used over time may therefore reflect changes in the antimicrobial class used, rather than changes in the number of treated animals. Inspired by the Defined Daily Dose in human medicine, the Animal Daily Dose (ADD) was created in 2004 in order to adjust for variation in potency between drugs.

(One) ADD is defined as the average maintenance dose for the main indication in a specified species.

(Jensen et al., 2004)

ADD can be calculated as ADD_{kg} or as ADD for the given age group. ADD_{kg} corresponds to the total body mass of one or more animals (of a specified species) that can be treated with the given amount of drug, and is calculated as the weight of the drug divided by the recorded dosage per kilogram of the animal. Dividing ADD_{kg} by the standard weight for the age group of interest results in the number of ADD. Standard weights have been defined as the expected weight at treatment. For pigs, these weights are: 15 kg weaners, 50 kg finishers, and 200 kg sows/boars (including piglets), resulting in ADD_{15}, ADD_{50} and ADD_{200} respectively (Jensen et al., 2004). The standard weights for cattle have changed slightly since the publication by Jensen et al. (2004). The categories "calves <12 months" (100 kg) and "heifers, steers" (300 kg) have been combined into one single category, "calves, heifers and steers", with a standard weight of 200 kg. Cows have retained their standard weight of 600 kg (personal communication Erik Jacobsen, DVFA). This results in ADD_{200} and ADD_{600} for cattle.

In order to standardize the use of antimicrobials for comparison between farms, the number of ADD can be divided by the number of animal days at risk. Therefore, a complete calculation of the treatment incidence (TI) can be written as follows (Box 1):

$$TI = \frac{\text{Amount of product (mg)}}{dosage\ \left(\frac{mg}{kg}\right) * weight(kg) * \#\ animals * time\ period\ (days)} * 100$$

- Amount of product: The amount of drug purchased by a given farm in a specific time period for a specific age group.
- Dosage: The specific dosage of the product, as stated in VetStat. Dosages of combination products have been set according to approved doses and are therefore assigned one single dosage (Anonymous, 2014a). In addition, the prolonged effect of long-acting drugs is taken into account in their dosage (personal communication Erik Jacobsen, DVFA). This means that a long-acting drug like Draxxin (25 mg/ml) is administered in a single dose of 1 ml/10 kg with a clinical effect of five days, and in VetStat, this dosage is set five times lower at 0.2 ml/10 kg, so that each administered dosage is equivalent to five daily doses.
- Weight: Standard weights of the treated age group.
- # Animals: The number of animals in the specific age group for the given CHR number, as stated in CHR.
- Time period: The time period for which the antimicrobial purchase data were extracted.

This calculation quantifies the national Danish use of antimicrobials as ADD per 100 animals per day (ADD/100 animals/day) (Anonymous, 2016b). This estimate approximates the percentage of animals treated at the farm per day, or the percentage of days that the average animal has been treated during its stay on a given farm.

Box 1: Calculation of the treatment incidence (TI)

3.2 Definition of health

The word health originates from an old Germanic root and literally means *wholeness* (Boyd, 2000). Although WHO defines health as *a state of complete physical, mental and social wellbeing, and not merely the absence of disease*, no unequivocal definition exists in veterinary medicine (Gunnarsson, 2006). The concept of health cannot correspond solely to the presence or absence of disease since it is possible to have a disease without feeling sick or without pathological changes (e.g. lice or fleas), and in contrast, it is possible to have symptoms without being able to diagnose any disease (e.g. faintness or headaches) (Boyd, 2000) Based on a review of existing veterinary textbooks, Gunnarsson (2006) suggests five potential definitions of health in veterinary medicine:

1. Health as normality in terms of appearance and behavior.
2. Health as biological function. This definition is commonly seen by pathologists who perceive disease as changes in the structure and function of cells in the body.
3. Health as homeostasis. This long-established approach suggests that disease arises when there is interference in the equilibrium of the body.
4. Health as physical and mental wellbeing, as defined by WHO. However, Gunnarson (2006) questions whether this definition is applicable to farm animals.
5. Health as productivity. This definition is uncommon in literature, but may relate to the first definition of health, assuming that healthy animals will grow and reproduce.

In this thesis, the definition of health was based on the available information present in the registers. Due to the simplification of these data, the definition was restricted to the absence or presence of SPF pathogens (Manuscript II), evaluation of production and mortality parameters (Manuscript V) and antimicrobial diagnostic groups intended for treatment (Manuscript III and IV).

3.3 Definition of management

According to the Saunders Veterinary Dictionary, management is defined as the *technique, practice or science of managing or controlling; the skilful use of resources and time; the specific treatment of a disease or disorder* (Blood and Studdert, 1999). It therefore includes factors such as feeding, housing, transport, disease prevention, general handling, manager influence, breeding and culling policies (Blood and Studdert, 1999; Radostits et al., 2000).

In this thesis, we evaluated management factors present in the registers, including farm size, farm type, production type, SPF status (Manuscript II), change in treatment procedures (Manuscript III), patterns of purchase and vaccination (Manuscript IV). In addition, we evaluated factors that were not present in the registers, but were mentioned by successful producers as influencing antimicrobial use, e.g. presence in the shed, feeding, sorting and hygiene procedures (Manuscript V).

3.4 Databases

3.4.1 VetStat

In this thesis, detailed information from VetStat on antimicrobial purchase was used as a proxy for antimicrobial use at herd-level. Records in VetStat are recorded at the CHR level. Each drug is purchased for a specific age group and diagnostic group. Data were validated using mismatches between species, age group and diagnostic groups. Antimicrobials recorded by veterinarians (only for the veal calf study), were checked for systematic errors, and any obvious errors were corrected. These systematic errors usually included the registration of antimicrobial products by the same veterinarian where the amount had been multiplied or divided by package size. These errors are typically seen as a result of veterinary IT systems being completed incorrectly.

3.4.2 CHR

CHR data were used to retrieve information on geographic location, herd type and the number of animals in the different age categories. In cases where more herds were present at the same CHR number, they were aggregated at the CHR number.

Annual CHR data extractions were used in pig studies. Farms with changes in recorded information were excluded.

3.4.3 SPF

SPF data were extracted for the specific herds at two time points one year apart. Farms with changes in health status (according to the type of herd, as breeding herds and production herds follow different rules and testing schemes in the SPF system) or SPF-pathogen infection status were excluded. When analysing SPF data, one should be aware that SPF farms are only tested for the absence of pathogens. Therefore, once the farm tests positive for a specific pathogen and this pathogen is added to the SPF status, the farm is no longer tested for that pathogen. The following pathogens (and prevalence of farms testing positive for these pathogens in 2013) are found in the SPF register: Mycoplasma hyopneumoniae (67%), Actinobacillus pleuropneumoniae (serotype 2 – 17%, serotype 6 – 26%, serotype 12 – 50%), Porcine Reproductive and Respiratory Syndrome (PRRS; DK variant – 27%, vaccine variant – 20%), Brachyspira hyodysenteriae (0.3%), toxin-producing *Pasteurella multocida* (2%), *Sarcoptes Scabiei* var *Suis* (0%), *Haematopinus suis* (0%) (Kristensen et al., 2015).

In this thesis, herds with changed SPF status were excluded (Manuscript III), as these may have been exposed to changes in the occurrence of clinical disease or management procedures. In addition, SPF data were used to differentiate between breeding and production farm types (Manuscript II).

3.4.4 Meat inspection data

All animals slaughtered in Denmark are inspected (European Parliament, 2004), and pathological remarks are recorded at animal level (Anonymous, 2011). Post-mortem meat inspection data may indicate any disease to which the animal has been exposed throughout its life. However, the sensitivity of meat inspection remarks is generally low and is dependent on both the abattoir (Enoe et al., 2003) and disease category (Bonde et al., 2010).

3.4.5 The Danish Cattle database

The Danish Cattle database was used to retrieve information on movements. Data relating to the number of calves introduced, their average age at introduction, the length of time they spent in each farm, and whether or not farms purchased calves from markets or delivering traders were extracted or calculated based on this information.

4. Results

4.1 Manuscript I

Swine databases: Evaluation of their quality and potential use for integrated disease surveillance

Swine databases: Evaluation of their quality and potential use for integrated disease surveillance

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Article in preparation

Keywords

Disease surveillance, register data, databases, swine

Abstract

In Denmark, several public and industry-owned databases concerning veterinary practice and health exist. These databases record information in order to facilitate decision making at the herd or regional/national level. Assessing data quality is crucial to determine to what extent conclusions can be drawn based on data.
The aim of the present study was to evaluate system structure and data quality of existing public and private databases, which may be used in the surveillance of swine diseases. Seven existing Danish swine databases were evaluated: the Central Husbandry Register (CHR) - including the swine movement database (SMD), the national Danish database on drugs for veterinary use (VetStat), diagnostic databases from two laboratories, the Specific Pathogen Free (SPF) System, and the meat inspection database. Qualitative attributes describing data quality were adapted from the European Center for Disease Prevention and Control's guidelines for evaluating monitoring and surveillance systems. The attributes were evaluated based on structured interviews of 20 interviewees, with extensive experience with each if the selected databases.
The extent to which the databases can be used for disease surveillance and monitoring varies greatly. In summary, only the laboratory and SPF databases had the surveillance of swine diseases as their primary objective. Antimicrobial use at the herd-level is influenced by a number of other factors than disease, which makes it controversial whether or not VetStat data can be used in the surveillance of disease. Meat inspection has the advantage of being registered at the animal-level, but sensitivity may vary a lot between disease categories. In contrast, the CHR and SMD are concerned only with swine traceability, indicating the population at risk, and are often used to standardize swine disease occurrence at farm level or to evaluate the effect of trading patterns. A general finding was that the quality of the databases tends to improve, whenever their registrations were interrelated with other databases or had economic or legislative implications.

1 Introduction

Disease surveillance describes the ongoing process of assessing the health and disease status of a given population [1]. This definition implies that some form of directed action will be taken, if the data indicate a change in disease status. However, the ability of automated systems to detect changes in disease occurrence depends to a large extend on the choice of the data source [2].

Assessing data quality is important to ensure that data are representative of the target population [3] and that valid conclusions can be drawn.

In Denmark, several public and industry-owned databases exist in the veterinary field [4]. For swine, the public databases include: the Central Husbandry Register (CHR) - including the swine movement database (SMD), the national Danish database on drugs for veterinary use (VetStat), Veterinary practitioners register (VetReg), the Control data register – from welfare and drug inspections in swine herds, the Zoonosis register with data on Salmonella seroprevalence and laboratory data from the National Veterinary Institute – Technical University of Denmark (DTU-Vet lab). Industry-owned databases include the Specific Pathogen Free (SPF) System, data from the diagnostic laboratory at the Pig Research Center-SEGES (VSP-SEGES lab), the Specific Pathogen Free (SPF) System and the meat inspection database. All databases record information in order to facilitate decision making at the herd or regional/national level.

Data gathered for research purposes are often referred to as primary data, whereas secondary data are data, which have been collected with a different purpose such as evaluation, management, administration, control and surveillance [5].

Secondary data are increasingly being used for research purposes [6–9]. However, research studies based on secondary data are typically associated with analytical and interpretive limitations. Challenges relate to technical aspects, political requirements, and stakeholder interests, which might influence the quality of data and its acceptance by the industry for disease surveillance. Therefore, it is important to evaluate data, when pursuing alternative uses, such as disease monitoring and surveillance.

The aim of the present study was to describe the importance of evaluating system structure and data quality of existing public and private databases, which may be used in the surveillance of diseases in swine.

2 Materials and Methods

2.1 Data quality attributes

In 2014, the European Centre for Disease Prevention and Control (ECDC) published a technical document to support processes for assessing data quality and evaluating surveillance systems for public health in European member states [3]. These guidelines aim to support professionals working with surveillance data, in order to provide accurate and timely information for decision making.

Seven Danish swine databases were chosen as examples and evaluated based on a set of qualitative data quality attributes adapted from the ECDC guidelines to evaluate monitoring and surveillance systems [3]. The seven databases were: the CHR, the SMD, the

VetStat, the DTU-Vet lab, the VSP-SEGES lab, the SPF System and the meat inspection database.

Table 1 describes the attributes used to evaluate the databases and the proposed indicators. A structured questionnaire with open questions for each data attribute was designed and used during the interviews (Annex 1).

Table 1: ECDC data quality attributes and proposed indicators to evaluate data quality in seven Danish databases on swine.

Attribute	Proposed indicator
1. Completeness	a) Warnings given by the system in case of missing information b) Examples of missing information allowed by the system
2. Validity	a) External validity: description of checks and validation of the data delivered to the database. Further described whether (correct) registration is related to any economic aspects b) Internal validity: description of checks and validation of the data in the database c) Examples of coding errors found in the database and how data are introduced into the system (pre-defined codes, free text)
3. Timeliness	a) How often are data updated/registered b) How much time is required between data (input) and availability of data in the database c) How much time from data entry to its subsequence use
4. Representativeness	a) The proportion of the population covered by the system/database
5. Usefulness	a) Use of data for control or eradication programs b) Presentation of data in e.g. reports, summary statistics or others
6. Simplicity	a) Time required to enter registrations into the system b) Time to have access to/extract data
7. Flexibility	a) Possibilities and timeliness of the system to adapt to changes, such as introduction of new codes/variables b) Examples of situations where new codes/variables were introduced in the database
8. Acceptability	a) Potential challenges in using the database for monitoring swine diseases and its eventual implications b) Combining different data sources for monitoring swine diseases and its eventual implications.

2.2 *Selection of database experts and interviews*

A total of 19 individual and joint face-to-face interviews were made for each of the seven databases under investigation during November 2015 to January 2016. Additionally, 1 email interview was conducted in the same period.

A total of 17 interviewees provided input to the full questionnaire for a specific database, while 3 provided inputs to specific questions only. Hence, each database was represented by the interview of 2-4 interviewees. Interviewees were selected based on their level of experience and involvement in the databases, prioritizing people maintaining and using data.

The questionnaire and objective of the study were sent in advance to all interviewees. Representative questions for each of the specific data attributes were discussed among the authors (Annex 1). In addition, the questionnaire was pre-tested on two colleagues, who work with the databases.

The duration of the interviews varied from thirty minutes to one and half hour, depending on the interviewee. The interviewees were encouraged to express their knowledge, personal opinions and experiences with the data.

The interviewers took written notes of the answers during the interviews. Background information on the databases was gathered from literature search prior to the interviews, while documents and reports recommended during the interviews were retrieved afterwards.

3 Results

3.1 *Description of databases*

In the following sections, the use of the data evaluation framework established by the ECDC is used for the seven chosen databases, and it is shown how the framework can be extended to the veterinary field. The description of the databases is summarized in Table 2. Each database is then described individually, except the two laboratory databases (DTU-Vet Lab and VSP-SEGES Lab), which are compiled. Detailed information regarding the data flow within each database is provided in Annex 2.

Central Husbandry Register (CHR)

The CHR is the national Danish database on farm demographics. The CHR was established in 1993 with the aim of tracing animals [10] and meet the subsequent European legislation [11,12]. All locations, where animals are gathered (e.g. farms, herds, markets, assembly centers, abattoirs, rending plants, agricultural shows and common pastures), must be registered in the CHR. Each location has its own unique CHR number with registration of affiliated address and Cartesian geographical coordinates. There can be several herds on the same location with the same CHR number. A herd is defined as a group of animals of the same species at the same location with a common aim and owner and are identified by unique herd numbers [13].

Swine Movement Database (SMD)

The SMD is technically a subset of the CHR. The database was established in 2002 to fulfill the European legislation regarding the trade of bovine and swine in European countries [14,15]. The original purpose of the database was to ensure traceability of all swine in

Denmark. It is mandatory to register all movements of swine in Denmark. However, registrations of swine movements are made on batch level, in which a batch contains a number of animals moved from one location to another. Thus, it is not possible to trace swine movements on the individual animal level.

The national Danish database on drugs for veterinary use (VetStat)

All prescription-only drugs for production animals are registered in the national database VetStat. It is mandatory to register purchase of drugs, either passively (by pharmacies and feed mills) or actively (by veterinarians). The registrations include detailed information such as the date, prescribing veterinarian, receiving farm ID, species, age group, and clinical indication [16]. The database was implemented in the year 2000 for research purposes. Subsequently, the use of VetStat data expanded to assist health advisory services provided by veterinarians, which may use data to keep track of developments in drug consumption and for decision making. Furthermore, VetStat data have since 2010 been used by the authorities to restrict antimicrobial use at the farm-level in the Yellow Card program [17]. On several occasions VetStat has been presented to foreign delegations. In relation to export, VetStat may enhance trading agreements with other countries by documenting antimicrobial control.

DTU-Vet Lab and VSP-SEGES Lab

The DTU-Vet lab and VSP-SEGES lab conduct extensive diagnostic examinations of a wide range of swine diseases in Denmark. Both laboratories have collaborative protocols and perform diagnostic testing in parasitology, immunology, virology, bacteriology, histopathology and necropsies. The DTU-Vet lab is the reference laboratory for all notifiable swine diseases in Denmark, including Brucellosis, tuberculosis, swine vesicular disease, foot-and-mouth disease, classical swine fever, African swine fever and Teschen disease [18]. The frequency of testing depends on the monitoring and surveillance programs implemented at national scale, the SPF status of the herd, outbreak investigations and eradication programs. Both laboratories have systems to record information to track samples during the process and send results and invoices to clients. The data can be extracted and diagnostic results can be used for disease monitoring by the SPF System and the public authorities.

The Specific Pathogen Free system (SPF System)

The SPF system was created in 1971 to combine health information with commercial interests [19]. The SPF system defines a fixed set of rules for biosecurity, surveillance and swine movement between herds (SPF-SuS). The health status is defined based on regular laboratory diagnostic results and clinical visits performed according to SPF rules. The movements of swine between herds are restricted according to the health status. This means that farms are not allowed to receive animals from farms with lower SPF-status than itself.

Meat inspection

Since 1964, meat inspection records of swine slaughtered in Denmark have been registered in a database [21]. The original aim of the database was to ensure food safety and justify payment to the farmer. Subsequently, the aim has expanded to include animal health and welfare, to fulfill the EU legislation [22].

Table 2: Summarized features of seven Danish databases which may be used in the monitoring and surveillance of swine diseases in Denmark.

Feature	CHR	SMD	VetStat	Laboratory databases	SPF	Meat inspection
Year of implementation	1993	2002	2000	VSP-SEGES lab: 1988 DTU-Vet lab: before the 90s	1971	1964
Current objectives	Retrieve demographical information at farm level	Tracing swine	Research, assist veterinary practitioners, control antimicrobial usage	Diagnostic, monitoring and surveillance of livestock diseases in Denmark	Manage the health status of participating farms	Payment of farmers, Food safety, Animal health and welfare
Data providers	Farmers, VSP-SEGES[1] staff	Abattoirs, Export stables, Pick up places, Rending plants, Farmers	Pharmacies, Veterinarians, Feed mills	Farmers, Veterinarians, Abattoirs, Research institutes	Laboratories, Ear tag database Zoonosis Register	Abattoirs
Data entry	Online or through VSP-SEGES, Aarhus N.	Receiving farm, exporting farm (for exports only), Transport company	Apothecary, veterinarian, veterinary secretary or employee in the feed mill.	Laboratory technician or automatic system depending on the diagnostic test performed	Automatic data entry from the different data providers	Technician or veterinarian working in the abattoir.
Database administers	DVFA[2]	DVFA	DVFA	DTU Vet[3]/ VSP-SEGES	SPF Sus[4]	Classification Authority
Case definition	Geographic locations where swine are gathered at herd-level	Movement of a batch of swine Herd-level	Purchase records of prescription-only drugs Farm-level	Laboratory submission including sample(s) collected at individual and herd level	Farm Farm-level	Carcass Animal-level
Information available by case	Farm number Date of establishment and closure, Contact details of the owner, Veterinary praxis number, Animal species, Production type, Numbers of animals	Farm number of sender and recipient Date and time of movement, Number of swine moved, Registration number of vehicle, Number of the trade certification for the movement	Recipient (farm number) Date of purchase, Prescribing veterinarian / Practice, Product information, Amount of drug, Targeted animal species, age group and diagnostic group.	Farm number, Biological material, Date of collection, Date of reception of the sample and analysis, (Anamnesis), Analysis codes, Test results	Farm number, Laboratory results, Danish Standard, Movement data.	Orig. farm number, Gambrel number, Abattoir ID, Date of slaughter, Transporter ID, , Delivery number, Weight, Meat percentage, Sex, Slaughter remarks, Measure of blubber

Feature	CHR	SMD	VetStat	Laboratory databases	SPF	Meat inspection
Surveillance programs for specific diseases	NA	NA	NA	SPF diseases, Salmonella level, Notifiable diseases (OIE listed diseases)	Enzootic pneumonia, Pleuropneumonia, Atrophic rhinitis, Dysentery, Porcine Reproductive and Respiratory Syndrome, Mange, Lice	Notifiable diseases (OIE listed diseases)
Geographic coverage	National	National	National	Farms sending samples	Participating farms	Farms sending swine for slaughter in Denmark
Data collection	Compulsory	Compulsory	Compulsory	Compulsory for Salmonella and Notifiable diseases (OIE listed diseases)	SPF farms	Compulsory post mortem inspection at slaughter
Deliverables and outputs	Online (https://chr.fvst.dk) SEGES yearly report DVFA Animal Health annual reports	Online (svineflyt.fvst.dk/) Reports available on the website (farm-level)	Yellow Card program (farm-level), DVFA monthly statistics (national-level) [23], DANMAP yearly report (national-level) [24].	Quarterly and yearly reports on the number of diagnostic tests for specific pathogens and tests available online (http://www.vet.dtu.dk/Diagnostik/Aarsrapporter-for-diagnostik_overvaagning_beredskab))	Farm status available on the website (www.spfsus.dk) Annual statistics reports (internal)	Yearly report by the Classification Inspection

[1] VSP-SEGES: Pig research Center- SEGES.

[2] DVFA: Danish Veterinary and Food Administration

[3] DTU Vet: National Veterinary Institute – Technical University of Denmark.

[4] SPF Sus: Specific Pathogen Free system (company)

Table 3: Summarized data quality and system evaluation of three public databases on swine herds in Denmark.
Data quality is assessed based on eight attributes adapted from the ECDC guidelines.

Data quality attribute		CHR	SMD	VetStat
Completeness	1)	All variables need to be filled in.	All variables need to be filled in before data can be sent to the database, except for specific cases, see add2	A warning is generated if all information from a specific pharmacy is missing in the monthly registrations.
	2)		Specific possible missing variables: Vehicle number, number of dead swine/containers	Complete missing cases possible (for registrations by veterinarians) ID of the drug
Validity	1)	Pre-coded fields where possible; Retrieves information from the official road-register; Registrations as perceived by the farmer.	Retrieves information from CHR. Partly economic: movement to abattoirs and rendering plants	Free typing text Double checks of purchase in pharmacies Majority economic: purchase from pharmacies
	2)	Computer-generated checks, from where letters of notification are sent out.	Computer-generated checks, from where letters of notification are sent out; For export: The registration is validated against the Danish Transport Standard	Retrospective manual checks made by DVFA-employees once and a while
	3)	Number of weaners and finishers registered tends to be more imprecise than the number of sows registered.		
Timeliness	1)	Existing herds: Update at minimum once/twice yearly; Establishment of new herd, change of ownership, arrival of new type of swine: Register within 7 days; Cessation of herd: Register within 6 months.	Movement of swine must be recorded within seven days of movement	Data are registered at the time of purchase (veterinarians and pharmacies) or shortly after (veterinarians)
	2)	Online registrations are available instantly.	online registrations are available instantly	No later than the 10th in the following month
	3)	Instantly	Instantly	Up to two months: Summary statistics are made on data from the second previous month to ensure all data are present in the database at the time of calculation
Representa-tiveness		Mandatory for all geographic locations holding a minimum of one swine.	All movements of swine are mandatory to register.	All herds using prescription-only drugs are present in VetStat.
Usefulness		Traceability of animals; Risk-based selection of herds for diseases and welfare controls; Manure reports	Tracing back swine in an outbreak situation; Eradication and control programs at herd level.	Research; Control of antimicrobial usage; Assist Veterinary Health Advisory Services.

Data quality attribute		CHR	SMD	VetStat
Simplicity	1)	Farmers themselves or VSP-SEGES staff update information online	Farmers themselves or VSP-SEGES staff update information online Slaughterhouses upload data once a day	Pharmacists, veterinarians and feed mills introduce the data manually
	2)	Registrations are instantly available online (herd-level)	Registrations are instantly available	1-2 minutes (herd-level) Hours (national-level)
Flexibility		Introducing new variables requires a change in the Danish order and an agreement with the IT-company maintaining the system.	Introducing new variables requires a change in the Danish order and an agreement with the IT-company maintaining the system.	Introducing new variables requires a change of the Danish order. Inflexible.
Acceptability	1)	Infrequent updates Herd type defined by the farmer Number of especially weaner and finisher may deviate from actual number Precautions using CHR data as disease-measuring tool.	Precautions using SMD data as disease-measuring tool.	Incongruence between original aim and current usage of the database; Precautions using VetStat data as disease-measuring tool.
	2)	Widely used in combination with other databases to retrieve information on herd demographics.	Used in combination with other databases to retrieve information on animal movement, e.g. may be used to track spread of disease.	

Table 4: Summarized data quality and system evaluation of four private databases on swine herds in Denmark.
Data quality is assessed based on eight attributes adapted from the ECDC guidelines. The column “Laboratory” covers information from the laboratory at the National Veterinary Institute, Technical University of Denmark (public), as well as the laboratory at the Pig Research Centre-SEGES (private).

Data quality attribute		SPF	Laboratory	Meat inspection
Completeness	1)	The system generates emails reminding the farmer and veterinarians to collect samples.	Missing information is allowed for some of the variables. However, the systems will give warning messages if variables, such as ID and results are missing, not allowing to close the journal.	The amount of data received weekly by the Classification Inspection is compared to expected number of entries. Missing information on e.g. meat percentage may occur in up to 0.5% of the cases before a warning occur.
	2)	Free text field to enter comments/information regarding the herd.	For submissions made by other institutes, including experimental studies, the herd/farm ID is no necessary.	Complete missing cases possible: Unreadable delivery number tattooed on the ham or separation of the carcass from the gambrel. A maximum of six remarks can be registered per carcass
Validity	1)	Retrieves information from CHR and laboratory data automatically. Economic: SPF status influences the price of the swine sold by the farmer	Double checks at insertion of data by more people Retrieves information from CHR Pre-coded fields for data entry	Machine-generated values (meat quality) Pre-coded fields or free typing text (veterinary remarks), depends on the system in the abattoir
	2)	No validation of the data is made.	Integral quality documents including standard operating procedures (SOPs).	No double checks of the data.
	3)	Free text typing of names of the owner when emitting notifications.	Free text for some variables especially for pathology results.	Difference in sensitivity between abattoirs [24].
Timeliness	1)	Overnight	Continuously as the laboratory results are available.	Daily
	2)	Once a day, but may be corrected instantly during working hours.	Instantly.	The database receives registrations from all abattoirs daily / weekly (depending on the abattoir).
	3)	Instantly	The samples can be tested in the same day or take weeks. The bills with the results are sent in the same day or it can take several weeks depending on the diagnostic test performed.	Up to one week from slaughter until the farmer is payed.
Representativenes s		Results gathered for all SPF herds on a regular basis: 99% of the breeding animals, 78% of sows and 34% of finishers in Denmark.	80-90% of the total number of Danish commercial swine herds (estimated by the interviewees).	98% of all swine slaughtered in Denmark (estimated by the interviewees).

Data quality attribute		SPF	Laboratory	Meat inspection
Usefulness		Health declarations; Eradication and control programs at herd level.	Disease monitoring and surveillance; Outbreaks detection Eradication and control programs at herd level.	Provide information for stakeholders to make decisions on political relevant issues.
Simplicity	1)	Serology results from laboratories are introduced automatically in the system; Health status changed manually when needed and available on the website.	Serology results from VSP-SEGES are introduced automatically in the system; Serology results from DTU Vet included by hand; Results from necropsies and pathology results need some time to type the results.	Once registered at the slaughter line, remarks are automatically transferred to the database in the Classification Inspection; No further data handling.
	2)	Access to small amounts of cases: 1-2 minutes, access to large amount of cases: several minutes	Access to small amounts of cases: 1-2 minutes, access to large amount of cases: several minutes	Hours for download of large amounts of data
Flexibility		Easy to include new diseases and pathogens.	Database managed by DTU vet: easy to change the information system to include new variables. Database managed by a private company for VSF-SEGES: difficult and costly.	Requires a change of the Danish order and then agreement with the IT-company maintaining the system, which is costly. Further demanding to change the system at the abattoir and to instruct technicians and inspectors.
Acceptability	1)	Monitoring animals' diseases and plan control and eradication programs at the herd level. Precautions using SPF data as disease-measuring tool	Monitoring animal's diseases and plan control and eradication programs and enables to monitor specific herds Precautions using Lab data as disease-measuring tool	Estimate true prevalence, sensitivity and specificity when possible; Enables evaluation of macroscopic disease lesions on a large proportion of Danish finishers/sows Precautions using meat inspection data as disease-measuring tool
	2)	Input data provided by different databases.	Laboratory data has the potential to be merged with other databases, such as movement data and CHR (GIS systems)	

3.2 Database attributes

The assessment of data quality and system evaluation is presented for the public databases in Table 3 and for private databases in Table 4. The results represent opinions of the interviewees and an evaluation of the attributes as defined in Table 1.

As an example, the CHR database (Table 3) records information from all farms (representativeness). The database requires that all variables are entered (completeness) using pre-coded or free text fields, and the data delivered to the online platform is checked (validity). The number of animals in each farm is updated at minimum once or twice per year, whereas other changes, such as change of ownership, are recorded within 7 days (timeliness). The CHR data is currently used for traceability of animals, risk based disease and welfare controls, manure reports and control of antimicrobial usage (usefulness). The information is updated by farmers or SEGES directly on the online platform (simplicity). The introduction of new variables or changes requires changes in Danish ministerial orders and agreements with IT companies (flexibility). The interviewees mentioned that the CHR database is widely used in combination with other databases to retrieve information on the swine herd (acceptability).

4 Discussion

In this study, the data quality of seven Danish databases on swine was assessed in relation to their usefulness for monitoring and surveillance of disease. These databases were selected due to extensive use by the Danish swine industry and research institutes.

4.1 Methodology

In order to structure the evaluation of the databases, the ECDC guidelines [3] were adapted to meet the requirements of veterinary databases. A full quantitative assessment would require extensive resources, including IT experts, to quantify each ECDC attribute for a large number of variables. Therefore, we opted for a qualitative approach to standardize the evaluation of seven diverse databases. The use of the qualitative approach was found useful, despite that some problems with the databases were not covered in the evaluation. For example, changes in regulations or other factors influencing the content of the databases were not covered in the analyses. Still, it is of utmost importance to be aware of such changes before data are analysed over longer time periods.

Other analytic approaches, such as SWOT (Strengths, Weakness, Opportunities and Threats) analysis [25], could be used for evaluation of databases. However, the ECDC guidelines were designed specifically to evaluate diseases surveillance systems and its data quality.

4.2 Data quality attributes

CHR and SMD

In relation to acceptability, CHR data are used extensively in combination with other databases, for example swine movements, retrieval of information on herd demographics for the laboratory data, standardization of antimicrobial usage [17], and selection of farms for risk-based farm-visits evaluating welfare [26]. Inter-correlation of databases may have the advantage of minimizing the risk of typing errors. However, it also means that incorrect information in one database is reproduced in the others. Since, CHR is used as reference-data for other databases, it is of paramount importance for these data to be correct. A number of automatized procedures have been implemented to secure completeness and validity of CHR data (Table 3). However, the classification of production type is registered as perceived by the farmer, which may lead to misclassification bias. One farmer may define the herd as a production herd, while the other would call it a hobby herd. As a consequence, using this classification to identify target farms for diseases monitoring and surveillance can be biased.

Regarding representativeness, differences occur when CHR data are compared to data from for example Danish Statistics, regarding number of animals and numbers of herds. More herds are registered in CHR, compared to other registers. This is because all non-closed herds are registered in CHR, while e.g. Danish Statistics do quarterly counts of active swine herds. (http://www.dst.dk/en/Statistik/dokumentation/documentationofstatistics/pigs/statistical-presentation)

Regarding timeliness in the CHR, the frequency of updates is irregular. According to legislation, the minimum frequency of updates is once or twice yearly (depending on the farm size) (Table 3). However, the farmer is allowed to update more often, which may lead to diversity in the precision of registration between farms. According to the interviewees, imprecision in number of swine is of concern, especially for weaners and finishers, while the numbers of sows tend to be more reliable. Also, CHR data is related to the manure account, where the number of animals must correspond to the area of land use [27]. However, when CHR data is compared to data from Danish Statistics, differences still exists, probably caused by the presence of all non-closed herds in CHR. On the other hand, despite the fact that all farms and all movements should be registered in CHR, it was not possible to estimate the coverage of these two registers. However, in Denmark there is a general belief in authorities, including an acceptance of the need to register in public databases. In addition to the use of the CHR-number for many purposes, such as veterinary prescriptions, we must assume that farms not registered are few, small and of limited importance.

Vetstat

In relation to VetStat acceptability, the amounts of registered antimicrobials may be used for treatment of other diseases than the one specified in VetStat. Furthermore, prescriptions are related to a certain age group, and each age group covers a wide variation in body weight. As the calculation of standardized measures of antimicrobial usage (in Denmark ADDs) includes measures of body weight, this variation highly influences the calculated ADDs. Additionally, the usage of antimicrobials by the farmer is influenced by factors not related to the level of disease, such as changes in legislation [28], prices of products [29], campaigns run by the pharmaceutical companies and the personal threshold for initiation of treatment. Therefore, the use of VetStat in disease surveillance can be controversial, when it is simultaneously used as a control tool.

DTU-Vet lab and VSP-SEGES lab

For laboratory data, the validity may be compromised by limitations in the system, specific changes or untrained persons entering the registrations. Especially, a wide variety of issues related to coding may occur, such as errors, variation throughout time, incompleteness [5], and variation in sensitivity and specificity of diagnostic tests. Moreover, changes in the representativeness over time depend on ongoing monitoring and surveillance programs implemented at national scale, outbreak investigations and eradication programs. Moreover, in veterinary science the frequency of testing depends also on the value of the animal and not only on the disease impact [30].

SPF system

The SPF system is a good example on how laboratory diagnostic information can be automatically integrated with variables from other databases. However, in relation to representativeness, this system only covers herds registered in the SPF System. The SPF has often been used as an expression of high health/good biosecurity. However, the opposite is not necessarily true for non-SPF herds, since farms can adopt SPF biosecurity rules, such as purchase of animals from SPF herds only and good external biosecurity, disregarding the serological testing for SPF diseases.

Meat inspection

In relation to validity, a low sensitivity of meat inspection has previously been shown [31], possibly caused by variation in clinical stage of cases presented at slaughter [25]. Since the reformation of slaughter codes in 2009 [32] courses were held targeting a standardized assessment of carcasses between abattoirs. However, courses may be needed regularly to maintain similar assessment. The variation might also be explained by variation in the configuration of terminals, where some abattoirs have pre-typed codes in the terminals, while digits need to be typed in separately in other abattoirs. In addition, the speed on the slaughter line leaves no time for double-checking, or retrospective updates. Furthermore, validity can be influenced by changes in staff and abattoir procedures [33]. Despite this, changes in codes [32,34] and legislative actions can influence the content of the database, which can complicate comparison of data throughout years.

General discussion

Comparison of observations over time is a key feature to incorporate these data into a surveillance system, since the existence of historical data for retrospective analysis is required by many statistical quality control methods used for disease surveillance in human and veterinary sciences [35–37]. It is therefore of utmost importance to be aware of changes in the databases, which may affect the attributes described in Table 3 and 4. In the CHR, the completeness and timeliness has definitely improved over time, as data collection has changed from a written mailed questionnaire of several pages to an electronic version online. Furthermore, validity has been improved by merging data from several sources and relating results to economic interests of the farmer. For example, VetStat and CHR have been combined and used in the Yellow Card legislation [17]. Farmers and veterinarians are now aware that incorrect information in one of these registers may entail that the herd exceeds the antimicrobial threshold value and is put under restrictions. In general, validity of databases tends to improve, whenever advantages of registration are visible to the farmer (SPF) or incorrect registrations have consequences (VetStat, CHR).

4.3 Perspectives

The extent to which the seven databases can be used as indicators of swine diseases varies. In agreement with their objectives, laboratory and SPF databases provide relevant data, which is used for monitoring diseases. However, both databases only include a selective proportion of the Danish swine herds, and the frequency of sampling varies between herds, which influence the capabilities of disease surveillance and monitoring. The use of sentinel surveillance [38] and investigation of unusual number of submissions or cases reported by veterinarians [39] might be possible approaches to overcome these issues. VetStat had surveillance of antimicrobial use for research purposes as its original objective. Assuming antimicrobial use is restricted to clinically diseased animals, VetStat data may also be used as a proxy for disease. However, a part of the antimicrobial use in swine production is used as metaphylaxis [40], which in addition to non-specific disease-categories in VetStat may compromise surveillance of specific diseases. Meat inspection has the advantage of being registered at the animal-level enabling tracing back and identifying the herd. However, the sensitivity is generally low and may vary between abattoirs [31] and disease categories [41,42]. Opposite, the CHR and SMD are confined to the traceability of swine, indicating the population at risk and to evaluate the effect of trading patterns. Moreover, clear guidelines regarding the categorization of herds on the registration page might minimize this type of misclassification in the CHR register.

As previously discussed, the validity of databases is improved when benefits or disadvantages are implemented. Another means of improving validity is by control strategies of data entrance, which may entail higher costs. This would need a prior cost-benefit analysis to document whether such initiatives pay off.

Nevertheless, the full potential of combining information from different databases for disease surveillance is yet to be explored. Combining such data might provide decision support for eradication and control programs. The limitations of the different datasets, addressed in the previous paragraphs, should be considered, when the data is used for the different purposes, such as research or surveillance activities. Furthermore, the changes of the described attributes over time should be taken into consideration. Thus, the use of databases for multiple purposes should be an iterative process; Identified limitations should be considered and addressed by the data owners in order to improve the quality and usefulness of data.

5 Conclusions

The present study described and evaluated the system structure of seven Danish swine databases, which are increasingly being used for research purposes. A general finding was that the quality of the databases tends to improve, whenever their registrations were interrelated with other databases or had economic or legislative implications.

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Annex 1- Questionnaire used during the interviews

System/database overview

1. What is (/was) the (original) objective of the database?
   a. Where is it described?
2. Which data sources are used? (vets, farmers, laboratory, etc)
3. For which purposes is this data being used?
4. Which diseases surveillance programs are based on this database? (NA is some cases)
5. Is the data gathered from all Danish pig herds?
6. Is the data compulsory/voluntary collected?
   a. if voluntary: Which type of farmers / economic advantages or costs related to participation?
7. Who is responsible for gathering the information? (data sources)
8. Who is the responsible for entering the data into the system? (data entry)
9. What information is exactly being recorded (where is it described)?
10. Who administers the database? (data operators)
11. Who has access to the database and who extracts the data? Is it the same person?
12. How is the data stored into the system? Integrated or relational? Is it connected to other databases (e.g. GLR-CHR-VetStat (and movement?) are apparently part of the same database)?
13. Are there any reports made based on the data?
    a. If so, how often are they made?

Completeness

14. Does the system give a warning if information is missing? For example, if you should collect information from 18 herds and you only have information for 4 herds?
15. Does the system allow “missing information”, when a registration is typed in?
16. Can you describe and give examples missing information from different variables for cases registered in the database?

Validity

17. Is there any person responsible for checking and validating the data delivered to the database compared with the case (external validity)?
    a. If yes, who? Data operator / manager? Same person every time?
    b. How often is it performed?
    c. What does this data check include (random or same check every time?
    d. In case of an error is found, which actions are taken?
18. Is there any person responsible for checking and validating the

data in the database (coding errors: internal validity)?
    a. If yes, who? Data operator / manager? Same person every time?)?
    b. How often is this performed?
    c. What does this data check include (random or same check every time?)?
    d. In case of an error is found, which actions are taken?
19. Which coding errors can be found in the database? Please give examples of variables with coding errors.
20. When data is entered into the database is it recorded using pre-defined codes used in the system (words) for all variables or is it "free" typing text/numbers?

Timeliness

21. How often is the database updated?
    a. Does this happen before / after eventual data checks?
22. How much time does it take between the data is available and is uploaded to the database?
23. How much time does it take from entry the data and its subsequent use?
24. Has the database been exposed to any major changes during the years, or is it possible to compare data throughout time?

Representativeness

25. What is the proportion of the population that is covered by the system? Could be expressed in numbers or percentages.

Usefulness

26. Can you indicate actions plans taken such as disease control/eradication programs based on the information originated from the system/database?
27. Is the data being used for specific purposes such as reports, research or other?
    a. Are these in agreement with the original purpose of the database?

Simplicity

28. How much time does it take to load the data into the system?
29. How much time does it take to have access to the data in the system?

Flexibility

30. How easy/time requiring is it to adjust information in the system?
31. Is it possible to add new codes/variables into the system?
32. Can you please give examples of situations where new codes/variables were introduced in the database? And which implications did it have? (if it was needed to create a completely new system)
33. How easy/time requiring is it to expand the system to for instance include new data (new variables)?

Acceptability

34. Do you think that these data can be used for monitoring pig diseases?
35. Do you think that is it possible to combine these data with other databases for monitoring pig

diseases? Eventual implications combining with other databases?

Annex 2 – Dataflow in the databases

Central Husbandry Register

It is the responsibility of the herd owner to register and keep registrations updated. Depending on the size, existing herds need to update their registrations once or twice a year. The latter only concerns large herds, e.g. for swine herds >300 sows, >3000 finishers or >6000 weaners [13]. Establishment of a new swine herd or inset of swine in an additional age group needs to be registered within 7 days, and closure of a herd no later than 6 months after removal of the last swine.

Farmers can register online [43] or ask SEGES, Aarhus N, to do it for them. The majority of data are instantly public available on the website. Computer-generated logical checks and follow-up letters are performed on a daily/weekly basis on registrations in the database. Examples on such checks include: Swine herds holding swine, but without movements or swine herds with neither registered swine nor movements.

Swine Movement Database (SMD)

Data can be entered by upload of data or by entering data through an interface. Data is available instantly when entered through an interface, while uploading occurs twice a day. All movements must be recorded within 7 days after movement. The data can be corrected after entering by the person that entered the data or the authorities. The receiving farm is responsible for registration of the movements. However, in case of exporting swine outside of Denmark, the sending farm is responsible for the registrations.

In the SMD, the number of swine moved, date and time of reception of the swine, CHR and herd number of sender and recipient, registration number of vehicle and the number of the trade certificate for the movement are registered [15]. The trade certificate is an official document that follows the swine. Furthermore, movements of dead swine to rendering are recorded as number of containers (primarily used for weaners, swine from 7-30kg) or number of dead sows or dead finishers (swine from 30-100 kg) [15].

Reports on the movement on specific herd number are public available via the website [44].

VetStat

All purchased prescription-only veterinary drugs are registered in VetStat.

At arrival at the pharmacy or feed mill, the prescription of veterinary drugs is typed in free text and is automatically recorded in the system simultaneously with payment. Procedures in the pharmacies include double-checks of all delivered drugs. All registrations made by pharmacies are at the time of registration automatically transferred to the Danish Health Authorities, who separate human and veterinary registrations. Veterinary registrations are forwarded to an IT-company handling VetStat. However, the amount of records is not assessed, meaning that some registrations may not be delivered to VetStat until the 10th in the following month. A warning appears, if VetStat has not received any registrations from the largest pharmacies. Opposite, veterinarians and feed mills actively need to register records on purchased veterinary drugs. Veterinarians can do this in four different ways, and feed mills in two different ways (the two latter): 1) Through the IT-system of the veterinary practice, 2) Registration on paper send to DVFA, 3) Uploading a file on the VetStat website, 4) Registration directly at the VetStat website. Registrations for both veterinarians and feed mills need to be registered no later than the 10th of the following month of purchase. Initially, all data arrive the IT-company handling VetStat. It is then merged with CHR data for use in the Yellow Card calculations [17], and is subsequently reload into VetStat. Only herds with a health-counselling agreement [45] are included in the Yellow Card program [17]. Summary statistics are made on data from the second previous month to ensure all data are present in the database at the time of calculation.

Laboratory databases

After receiving the samples (organic material for analysis), the laboratory technicians are responsible for creating the journal (case file), including registration of sample ID, CHR number, farmer identification and veterinarian. The information entered is double-checked by another person. Depending on the diagnostic test performed and on the system, the results are transferred automatically to the system or entered manually. The academic staff is responsible for validating the results. Depending on the type of diagnostic test performed, the results are available on the same day (i.e. serology) or within several days/weeks (i.e. histopathology, bacteriology). The results are reported to costumers by email or letter. In case of missing results of individual samples, the system will give a warning and does not allow closure of the journal.

Danish Specific Pathogen Free (SPF) system

Laboratory diagnostic results from SPF-herds are retrieved automatically on working days from DTU Vet and VSP-SEGES. The system generates alarms, if the SPF-herds were classified as positive for a disease, which does not correspond to the current SPF herd status. In case of an alarm, the results are checked manually and decisions to change or keep the health status are made. Changes in the herd health status are, during working hours, updated immediately on the SPF website.

The SPF system also includes data on *Salmonella* for all Danish swine herds. For breeding and multiplier herds, the *Salmonella* index is calculated based on serological testing. For herds delivering more than 200 finishers annually, the Salmonella level is retrieved from the Zoonosis Register. The salmonella level is calculated each month by serological testing of “meat juice” (drip fluid released from meat after freezing and thawing).

The system also gathers data related to swine movements. A Danish animal trade company, SPF-Denmark (SPF-DANMARK), plans and perform swine movements, taking into account the SPF-status of the herds. The company provides information on the farmers name, addresses and the number of finishers and sows to the SPF register[1]. The number of weaners is retrieved from the ear-tag register. The system generates an alarm if animals from a

[1] Information on movements are also registered in the SMD.

certain health status are sold to herds with higher health status.

Furthermore, information about the Danish Standard (SEGES - Videncenter for Svineproduktion) is also available in the SPF system. The requirements of Danish swine farmers should correspond to the regulatory and industry requirements. These requirements are described in the Danish Product Standard. An independent company carries out audits (inspections) in the herds. This information is also available in the SPF-website and includes 100% of all Danish swine herds.

Meat inspection

At arrival in the abattoir, all swine are checked *ante mortem* by the official veterinarian to determine cases of welfare violation or signs of OIE-listed diseases [22].

After slaughter, each carcass is associated with a specific gambrel number, to which the following information is registered: Abattoir ID, date of slaughter, transporter ID, originating CHR number, delivery number, carcass weight, meat percentage, price, sex, up to ten (six in practice) different veterinary slaughter remarks, measure of fat depth, meat and if necessary skatole (boars only). The delivery number is used to identify the herd of origin at all times during the slaughtering process.

The majority of registrations are measured and registered automatically. Only veterinary slaughter remarks are registered manually by the technician on the slaughter line or the veterinarian at the site of re-examination.

4.2 Manuscript II

Persistent spatial clusters of prescribed antimicrobials among Danish pig farms – a register-based study

PLOS ONE

RESEARCH ARTICLE

Persistent Spatial Clusters of Prescribed Antimicrobials among Danish Pig Farms – A Register-Based Study

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Data Availability Statement: Data used in the study are owned by a third party and can therefore not be made publicly accessible. Interested researchers can access data in the same way as the authors of this manuscript did, by contacting: Thorkild Bastholm: tob@fvst.dk (CHR data) Erik Jacobsen: erja@fvst.dk (VetStat data) Bent Nielsen: ben@seges.dk (SPF data).

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Abstract

The emergence of pathogens resistant to antimicrobials has prompted political initiatives targeting a reduction in the use of veterinary antimicrobials in Denmark, especially for pigs. This study elucidates the tendency of pig farms with a significantly higher antimicrobial use to remain in clusters in certain geographical regions of Denmark. Animal Daily Doses/100 pigs/day were calculated for all three age groups of pigs (weaners, finishers and sows) for each quarter during 2012–13 in 6,143 commercial indoor pig producing farms. The data were split into four time periods of six months. Repeated spatial cluster analyses were performed to identify persistent clusters, i.e. areas included in a significant cluster throughout all four time periods. Antimicrobials prescribed for weaners did not result in any persistent clusters. In contrast, antimicrobial use in finishers clustered persistently in two areas (157 farms), while those issued for sows clustered in one area (51 farms). A multivariate analysis including data on antimicrobial use for weaners, finishers and sows as three separate outcomes resulted in three persistent clusters (551 farms). Compared to farms outside the clusters during this period, weaners, finishers and sows on farms within these clusters had 19%, 104% and 4% higher use of antimicrobials, respectively. Production type, farm type and farm size seemed to have some bearing on the clustering effect. Adding these factors as categorical covariates one at a time in the multivariate analysis reduced the persistent clusters by 24.3%, 30.5% and 34.1%, respectively.

Introduction

In Denmark, 29 million pigs are produced annually accounting for 76% of prescribed veterinary antimicrobials [1]. There has been an increase in public awareness surrounding the prudent use of veterinary antimicrobials due to the emergence of antimicrobial resistance [2,3,4].

Subsequently, a number of legislative actions targeting a reduction in the use of antimicrobials for pigs have been launched in Denmark [5,6,7,8].

Antimicrobial treatment of production animals is, according to Danish legislation, restricted to clinical disease, thus excluding use for prophylaxis and growth promotion [9]. In Denmark, the three age groups of pigs, for which antimicrobials are prescribed are: weaners, finishers and sows (including boars and piglets). The consistency in the overall antimicrobial consumption at a farm is therefore ideally assessed using a multivariate analysis combining the use in all three groups simultaneously. The primary clinical reasons for prescribing antimicrobials are gastrointestinal and respiratory disorders for weaners and finishers, and limbs/joints/CNS/skin and urogenital disorders for sows [10]. Management and medication practices vary substantially among Danish pig farmers. The choice of drug, dose and treatment time as well as the perception of metaphylaxis all influences the administration of antimicrobials at the farm.

For sow farms, densely populated areas have been found to have a higher use of antimicrobials than sparsely populated areas [11]. Furthermore, the amount of antimicrobials prescribed for gastrointestinal disorders in finishers has been found to be highly affected by geographical region [12]. Additionally, treatment practices on farm has been shown to remain stable over time [13]. Due to variation in farm density, veterinary affiliation and a presumed stability in treatment practices on farm, our hypothesis was that a number of persistent spatial clusters exist in the amount of antimicrobials prescribed for pigs. Thus, the objective of this study was to identify and characterize the spatial clusters of Danish indoor commercial pig producing farms that persistently prescribed significantly more antimicrobials during 2012–13.

Materials and Methods

Study design

The study was designed as a register-based study on antimicrobial use during the years 2012 and 2013. Data from all indoor commercial pig farms were included in the study, with the exception of those excluded due to recording mistakes (Fig 1).

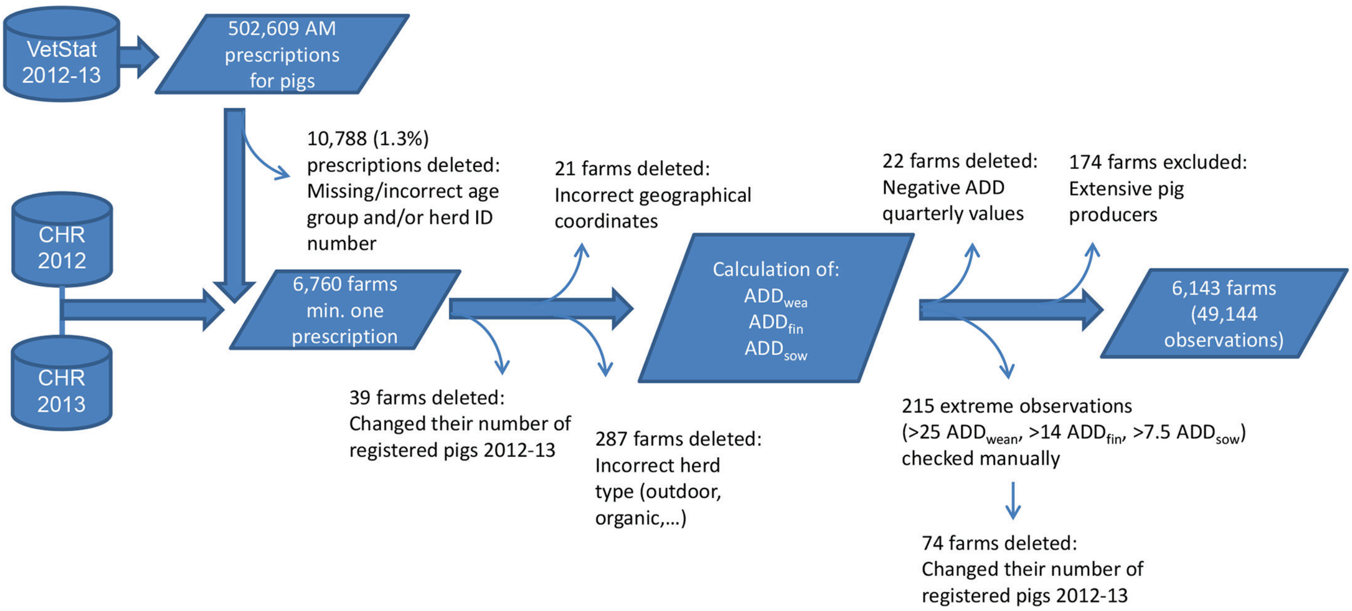

Fig 1. Flow diagram of data management. Data extracted from the Danish national databases VetStat and CHR were used to calculate up to three standardized measures of antimicrobials for each pig farm (ADD_{wea}, ADD_{fin} and ADD_{sow}). AM = antimicrobials.

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Study population

A total of 6,143 farms were included in the study population and were characterized in terms of their Cartesian coordinates for geographic location, farm type (production/nucleus), type of production (presence of one or more age groups), farm size (number of pigs, separately evaluated for each of the three age groups) and Specific Pathogen Free (SPF) status. To insure that only active farms were included in the study, a minimum of one prescription during the two-year study period was required (6,760 farms). Reasons for exclusion were missing (19 farms) or identical Cartesian coordinates (2 farms), changes in farm size (39 farms), farm type (e.g. outdoor, organic, boar stations) (287 farms), negative antimicrobial values in one of the quarters (22 farms) and extensive pig producers (174 farms) with fewer than 50 sows, 200 finishers and 200 weaners (Fig 1).

Production farms (5,915 participating) are defined as farms producing weaners and/or finishers, while nucleus farms (228 participating) are defined as farms only producing breeding stock [14]. Farms participating in the voluntary SPF system have a certain level of biosecurity and are aware of the on-farm infection status of two specified ectoparasites and five pathogens [15]. Data from the SPF system were extracted in March 2013, while data on farm demographics were retrieved from the Central Husbandry Register (CHR) in January 2012 and October 2013.

Antimicrobial prescription

The quantity of antimicrobials prescribed at a given farm was assumed to be a consistent proxy for the level of consumed antimicrobials during the given time period. Since 2000, all veterinary antimicrobial prescriptions for production animals have been recorded in the national Danish database, VetStat [16]. VetStat receives information from three sources: Feed mills, veterinarians and pharmacies. For pigs, more than 98% of the total number of prescriptions for pigs is recorded by pharmacies. To avoid the influence of legislative initiatives [17,18], we did not include data prior to January 2012. This study used prescriptions issued by pharmacies from the period of 1st January 2012 to 31st December 2013; in total 844,704 prescriptions of where 502,609 were antimicrobial prescriptions (Fig 1). Registrations were retrieved from VetStat on 31st March 2014. Each prescription contained detailed information on the prescription date, prescribing veterinarian, recipient (farm number), animal species, age group, clinical indication, antimicrobial product and amount of antimicrobial [16,10]. However, 10,788 (1.3%) prescriptions were deleted due to a missing (or incorrect) age group (10,674) and/or farm identification number (132).

Antimicrobials were assessed as Animal Daily Doses (ADD). One ADD is defined as the dose needed to treat one pig of a given size for one day for the main indication. VetStat uses standard weights for treatment in each of the three age categories: 15 kg (weaners), 50 kg (finishers) and 200 kg (sows, boars and piglets). One ADD_{15} equals one standard dose needed to treat one standard weaner (15 kg pig) for one day. Likewise ADD_{50} and ADD_{200} are calculated for finishers and sows. The number of ADDs aggregated on the farm level for each of the three age groups was divided by the number of pig days at the farm. The number of registered pigs in each of the three age groups was extracted from the CHR register and multiplied by the number of days in the given time period, to calculate the total number of pig days at risk. This standardized unit is consistent with the official unit: Prescribed number of ADD per 100 pigs per day (ADD/100 pigs/day), which approximates the percentage of pigs treated at the farm daily [7,19]. Therefore, up to three estimates were calculated per farm: ADD_{15}/100 weaners/day, ADD_{50}/100 finishers/day and ADD_{200}/100 sows/day, denoted here as ADD_{wea}, ADD_{fin} and ADD_{sow}, respectively. These standardized measures enable comparison across farms, despite variations in farm size and choice of drug [19]. In VetStat, each antimicrobial product was initially assigned an appropriate dose based on pharmaceutical approval. In 2014, the doses were revised [7]. For this project, results are presented using the new doses.

Most pig farms have a health counseling contract, which includes visits by a veterinarian 9–12 times a year (4–6 times a year for finisher-only farms) [9]. Drugs are typically prescribed in connection with such visits. In support of this, Vigre et al [20] identified the median duration of prescription period to be 36 days for weaners and 39 days for finishers. Therefore, prescribed antimicrobials were aggregated quarterly for each of the three age groups to reflect the actual use of antimicrobials within a given time period.

The three right-skewed continuous distributions, ADD_{wea}, ADD_{fin} and ADD_{sow}, were log-transformed to reduce the influence of extreme values. A relatively large number of the observations were zero (13% sows, 19% weaners and 28% finishers). To allow transformation despite the observations of zero, a small constant was added to the total amount of prescribed antimicrobial at each farm. This constant was added prior standardization and transformation, so that a zero observation in a large farm was assigned a smaller value than a zero observation in a small farm. The added value equaled half the smallest amount of prescribed antimicrobials during the first quarter corresponding to 29 ADD_{15} for weaners, 6.5 ADD_{50} for finishers and 1 ADD_{200} for sows.

Spatio-temporal analyses

The scan statistic can be used in the identification of local clustering of an event in space and time. Traditionally, the procedure has been used to investigate clustering of disease in human as well as veterinary epidemiological studies. Scan statistic is based on a circular scanning technique using the log likelihood ratio test [21]. Recently, the univariate scan statistic has been extended to include continuous outcomes [22] and may incorporate multiple datasets (e.g. different diseases or different population characteristics) [23]. This multivariate scan statistic method has so far only been sparsely applied in veterinary epidemiology [24]. To our best knowledge, this is the first study in veterinary epidemiology to make use of a multivariate scanning technique with a continuous outcome.

Here, we made use of both the scan statistic methods (univariate and multivariate) to test whether the mean of ADD_{wea}, ADD_{fin} and/or ADD_{sow} in Danish commercial indoor pig farms was higher in certain geographical areas throughout time than would be expected due to chance. To allow for unrestricted geographical overlap of clusters in different time periods, repeated spatial analyses were performed, rather than a single spatio-temporal analysis. To increase the study power the scan statistic was ran on a six-month scale; hence, each analysis included two observations per age group at a farm, one for each quarter. The geographical areas included in a significant cluster in all four consecutive time periods were defined as a persistent cluster. Following this, the total number of farms within the intersection of the four significant clusters was identified.

Purely spatial retrospective analyses were executed using a normal probability model [22]. Initially, univariate models were run for each of the three outcomes separately: $Ln(ADD_{wea})$, $ln(ADD_{fin})$ and $ln(ADD_{sow})$. Subsequently, by including all three datasets ($ln(ADD_{wea})$, $ln(ADD_{fin})$ and $ln(ADD_{sow})$), a multivariate version of the model [23] was used. Additionally, three categorical covariates (production type (7 levels), farm type (2 levels) and farm size (3 levels)) were added one at a time to the multivariate model, in order to investigate the effect on clustering.

The maximum spatial cluster size was set to 20% (1,229 farms) of the population at risk. No geographical overlap was allowed in the individual analyses. An elliptic spatial shape was selected to account for edge effects of the estimated cluster areas. However, the exact borders of the underlying true clusters remain uncertain regardless of the shape used [25].

For each of the generated elliptic windows (e.g. scanning windows) around each location, the log-likelihood for observing a higher mean ADD value within the window was calculated. The window with the maximum log-likelihood was identified as the most likely (or primary) cluster. The distribution of log-likelihood ratio statistic under the null hypothesis was evaluated using Monte Carlo hypothesis testing. In the multivariate analysis, clustering which occurred in a single dataset or in more datasets simultaneously was evaluated. This was achieved by establishing a combined log likelihood defined as the sum of log likelihoods from each of the individual datasets where the observed antimicrobial use exceeded the expected use [23]. Significant ellipses ($p<0.05$) contributing to a persistent cluster were plotted on a map. A chi-square test was applied to test whether farm characteristics were significantly different inside compared to outside the clusters.

Data management was carried out using the software SAS [26]. Subsequently, data were exported to R [27], for statistical analysis. Spatial analysis was carried out in SaTScan [28].

Results

As illustrated in Fig 2, the farm density of participating farms is generally higher in the western part of Denmark than the eastern part.

Based on data from the CHR and from the SPF register, farms included in the analyses are described by their SPF status, production type, and farm size (Table 1).

Prescribed antimicrobials standardized as ADD_{wea}, ADD_{fin} and ADD_{sow}, for each quarter of 2012 and 2013 in the 6,143 study farms are presented in (Table 2). Depending on the production type, each farm held information on up to three measurements of antimicrobial consumption (one for each age group of pigs). The variable 'production type' had seven levels, defining the presence or absence of the three age groups of pigs. Farm size was categorized according to the quartiles for each of the three age groups: Small (<Q1), Medium (Q1 –Q3) and Large (>Q3). Information on farm type, production type and farm size were complete for all 6,143 farms and were used as covariates in the multivariate model.

Two persistent clusters were identified by the univariate cluster analysis on antimicrobials prescribed for finishers. These clusters included 99 and 58 farms, respectively (Fig 3). On average, finishers inside these persistent clusters consumed 158% more antimicrobials (2.01 ADD_{fin}) than finishers outside the clusters (0.78 ADD_{fin}) (Table 3). Likewise, a univariate model on antimicrobials prescribed for sows resulted in one persistent cluster of 51 sow farms (Fig 4) consuming 38% more antimicrobials (2.49 ADD_{sow}) compared to sow farms outside the clusters (1.80 ADD_{sow}) (Table 3). The univariate analysis on antimicrobials prescribed for weaners did not result in any persistent clustering.

The multivariate analysis resulted in three persistent clusters, including 33, 209 and 309 farms respectively (Fig 5). In these clusters, the antimicrobial consumption was 19% higher for weaners, 104% higher for finishers, and 4% higher for sows (Table 3). Characteristics of farms inside and outside these clusters are presented in Table 4. The distribution of weaner and finisher farm sizes was significantly different inside compared to outside the clusters (Table 4).

The three multivariate persistent clusters were geographically close to the three persistent clusters found in the univariate analyses. One sow farm and 99 finisher farms were included in the univariate as well as the multivariate persistent clusters, which meant that 50 sow and 58 finisher farms were included in the univariate persistent clusters, but omitted from the multivariate persistent clusters.

Adding the three covariates farm type, production type and farm size one at a time to the repeated multivariate cluster analysis reduced the number of farms inside the persistent clusters to 383 (30.5%), 417 (24.3%) and 363 (34.1%), respectively.

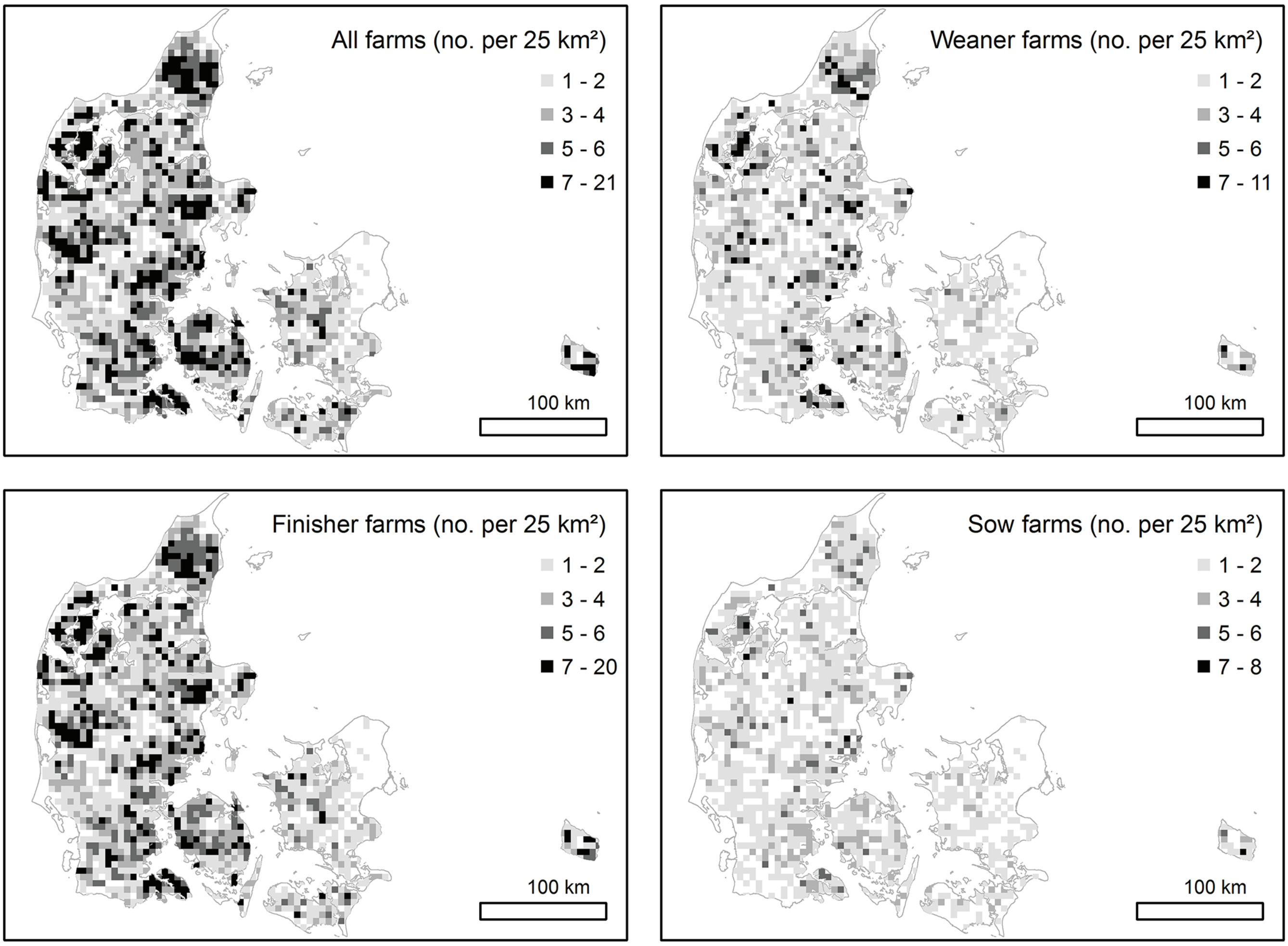

Fig 2. Map of the Danish indoor commercial pig farm density. "All farms" illustrate the geographical distribution of all 6,143 indoor commercial pig farms in Denmark. Maps denoted "weaner farms" (2,886), "finisher farms" (5,417) and "sow farms" (2,062) illustrate farms holding the respective age groups. Colors indicate number of farms present in each square (5*5 kilometer).

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Discussion

This study describes how the use of antimicrobials in indoor commercial pig farms persistently cluster in certain geographical areas compared to farms in the rest of Denmark.

Clusters of antimicrobials prescribed for sows seemed to remain more constant (Fig 4) than antimicrobials prescribed for finishers (Fig 3) or for all age groups (multivariate analyses) (Fig 5). The main indications for use of antimicrobials in sows/piglets include urogenital and limbs/joints/CNS/skin disorders [10]. In practice, these conditions are typically seen as metritis-mastitis-agalactica and arthritis, respectively [29]. Feeding and stable facilities seem to play a critical role in the prevalence of both conditions [30] and represent parameters which are not expected to change markedly over time. Contrary, a large variability was found for finishers (Fig 3) and especially weaners, where no persistent clusters were detected. Gastrointestinal disorders (*Lawsonia intracellularis*, *Brachyspira* spp. and *Escherichia coli*) and respiratory disorders (*Actinobacillus pleuropneumoniae*, *Pasteurella multocida* and *Streptococcus suis*) [10] are the primary causes of treatment for weaners and finishers. Due to the infectious origin of both

Table 1. Characteristics of 6,143 Danish indoor commercial pig producing farms, based on data from 2012–13.

Farm characteristics		Numbers of farms (%)
Conventional vs SPF status	Conventional farms (non-SPF)	3,419
	Farms in SPF register	2,724
Production type(age groups present at the farm)	Farrow-to-finisher	1,430 (23.3)
	Sows and finishers	159 (2.6)
	Sows and weaners	288 (4.7)
	Sows	185 (3.0)
	Weaner and finishers	915 (14.9)
	Weaners	253 (4.1)
	Finishers	2,913 (47.4)
Farm size		
Presence of sows*	Small (1–254)	513 (24.9)
	Medium (255–670)	1,043 (50.6)
	Large (> 670)	506 (24.5)
Presence of weaners*	Small (1–783)	722 (25.0)
	Medium (784–2300)	1,458 (50.5
	Large (> 2300)	706 (24.5)
Presence of finishers*	Small (1–499)	1,342 (24.8)
	Medium (500–1600)	2,769 (51.1)
	Large (> 1600)	1,306 (24.1)

*One farm may appear in multiple categories of farm size if more age groups are present at the farm.

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conditions they typically require treatment of a high proportion of pigs. Farm density is expected to have a significant effect on the transmission of airborne pathogens, and has previously been positively correlated to an increased frequency of antimicrobial treatments for sows [11], and respiratory treatments in finisher farms [31]. In general, the density of farms included in the study population was higher in the western part of Denmark than in the eastern part (Fig 2). Especially, clusters from the multivariate analysis seemed to coincide with local regions with high farm density in the western part of Denmark. However, other factors than farm density does seem to have an additional effect on the use of antimicrobials, since regional variation in farm density did not seem to coincidence with all persistent clusters (Figs 2, 3, 4 and 5).

Table 2. Median and interquartile ranges of the amount of prescribed antimicrobials for three ages groups for each quarter in 2012–13 in 6143 Danish indoor commercial pig producing farms.

		Weaners $\mathbf{ADD_{wea}}$ **[IQR]**	**Finishers** $\mathbf{ADD_{fin}}$ **[IQR]**	**Sows** $\mathbf{ADD_{sow}}$ **[IQR]**
2012	Jan–Mar	8.47 [2.72;14.64]	0.97 [0.04;2.88]	1.92 [1.07;2.98]
	April–Jun	8.05 [2.06;14.63]	0.76 [0.00;2.66]	1.77 [0.96;2.78]
	Jul–Sep	7.44 [1.70;13.61]	0.76 [0.00;2.65]	1.69 [0.88;2.68]
	Oct–Dec	8.17 [1.76;14.40]	0.87 [0.00;2.79]	1.75 [0.88;2.75]
2013	Jan–Mar	8.10 [1.25;15.43]	0.82 [0.00;2.97]	1.92 [0.86;3.03]
	April–June	7.93 [0.99;14.92]	0.70 [0.00;2.75]	1.87 [0.81;2.99]
	Jul–Sep	7.53 [0.69;14.37]	0.69 [0.00;2.77]	1.79 [0.76;2.90]
	Oct–Dec	8.18 [1.12;14.83]	0.98 [0.00;3.12]	1.84 [0.75;2.91]

ADD = Animal Daily Doses per 100 animals per day.

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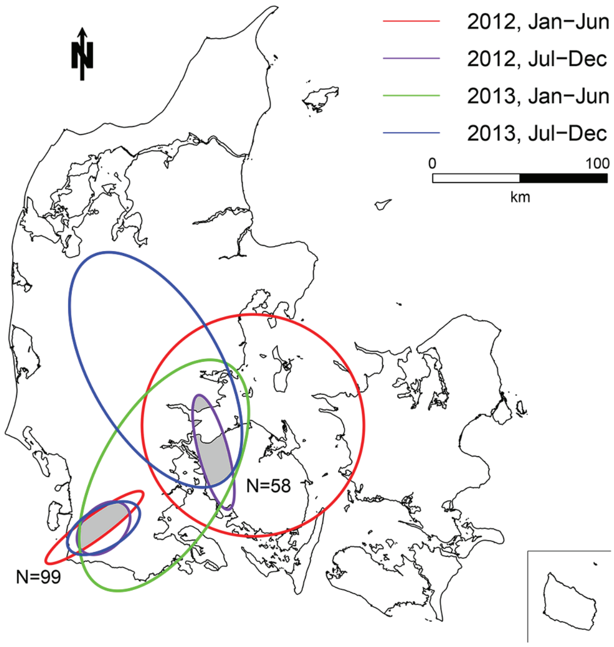

Fig 3. Map of the univariate persistent clusters of antimicrobials prescribed for finishers. Each ellipse illustrates a significant cluster (p<0.05) in one of the four time periods. Two persistent clusters were identified, including a total of 157 farms. N indicates the number of farms inside each of the persistent clusters.

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Pathogens of highest relevance within Denmark, and which may spread between pig farms in close proximity include: *Mycoplasma hyopneumoniae*, Swine Influenza Virus, Porcine Respiratory Syndrome Virus, Porcine Circo Virus type 2 and less commonly *Actinobacillus pleuropneumoniae* [32,33,34,35,36,37,38]. However, possible transmission between neighboring farms

Table 3. Median and interquartile ranges for antimicrobial use in 6,143 Danish pig farms inside and outside identified persistent clusters from 2012–13.

		No. of farms	ADD_{wea}[IQR]	ADD_{fin} [IQR]	ADD_{sow}[IQR]
All farms		6,143	7.99 [1.51;14.59]	0.82 [0.00;2.82]	1.82 [0.88;2.87]
Univariate models					
Antimicrobial for sows	Inside	51			2.49 [1.54;3.64]
	Outside	2,011			1.80 [0.87;2.86]
Antimicrobial for finisher	Inside	157		2.01 [0.52;4.21]	
	Outside	5,260		0.78 [0.00;2.78]	
Multivariate model	Inside	551	9.40 [3.97;15.93]	1.55 [0.13;3.57]	1.89 [1.06;2.94]
	Outside	5,592	7.88 [1.30;14.48]	0.76 [0.00;2.73]	1.81 [0.86;2.87]
+ Farm type*	Inside	383	10.47 [4.52;16.76]	1.74 [0.14;3.86]	1.97 [0.96;3.04]
	Outside	5,760	7.87 [1.38;14.47]	0.76 [0.00;2.74]	1.81 [0.88;2.87]
+ Production type*	Inside	417	9.97 [4.62;16.46]	1.55 [0.14;3.56]	1.87 [1.08;2.84]
	Outside	5,726	7.88 [1.30;14.48]	0.77 [0.00;2.75]	1.81 [0.87;2.88]
+ Farm size*	Inside	363	10.94 [5.09;17.16]	1.81 [0.18;3.94]	1.89 [0.99;2.94]
	Outside	5,780	7.87 [1.35;14.45]	0.77 [0.00;2.74]	1.81 [0.88;2.87]

*The regular multivariate model added one of the three covariates separately (farm type, production type or farm size).

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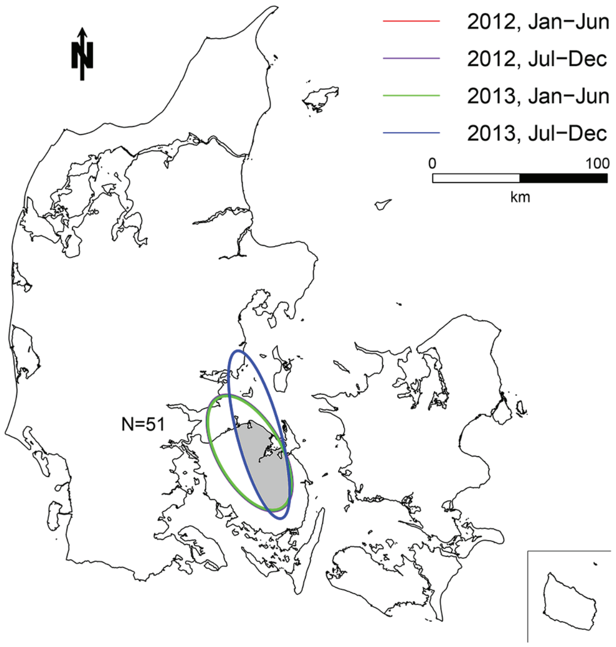

Fig 4. Map of the univariate persistent cluster of antimicrobials prescribed for sows. 51 farms located in one persistent cluster area. Each ellipse illustrates a significant cluster (p<0.05) in one of the four time periods. The three significant clusters from January 2012 to June 2013 lie on top of each other, which is why only two ellipses are visible. N indicates the number of farms inside the persistent cluster area.

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by vectors other than air [32] increase the spectrum of transmittable pathogens. Cold and humid weather conditions favor the survival of pathogens, which is why the risk of airborne

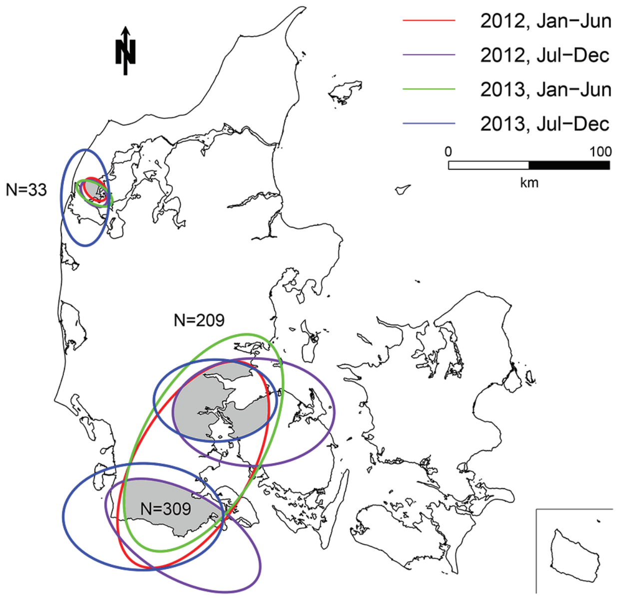

Fig 5. Map of the multivariate persistent clusters. Each ellipse illustrates a significant cluster (p<0.05) in one of the four time periods. The persistent clusters include a total of 551 farms situated in three distinct geographical areas. N indicates the number of farms inside each of the persistent cluster areas.

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Table 4. Characteristics of 6,143 farms inside versus outside the three multivariate persistent clusters.

		Farms inside clusters Actual No. (%)	Farms outside clusters Actual No (%)	p-value
Total number of farms		551 (9.0)	5,592 (91.0)	
Conventional farms		299 (54.3)	3,120 (55.8)	
Farms in the SPF register		252 (45.7)	2,472 (44.2)	0.519
Farm type	Nucleus farms	29 (5.3)	199 (3.6)	
	Production farms	522 (94.7)	5,393 (96.4)	0.057
Production type	Farrow-to-finisher	113 (20.5)	1,317 (23.6)	
	Sows and finishers	16 (2.9)	143 (2.6)	
	Sows and weaners	32 (5.8)	256 (4.6)	
	Sows	11 (2.0)	174 (3.1)	
	Weaner-finisher	72 (13.1)	843 (15.1)	
	Weaners	24 (4.4)	229 (4.1)	
	Finishers	283 (51.4)	2,630 (47.0)	0.155
Farm size				
Presence of sows	Small (1–254)	40 (23.3)	473 (25.0)	
	Medium (255–670)	97 (56.4)	946 (50.1)	
	Large (> 670)	35 (20.3)	471 (24.9)	0.247
Presence of weaners	Small (1–783)	48 (19.9)	674 (25.5)	
	Medium (784–2300)	143 (59.3)	1,315 (49.7)	
	Large (> 2300)	50 (20.7)	656 (24.8)	0.016
Presence of finishers	Small (1–499)	112 (23.1)	1,230 (24.9)	
	Medium (500–1600)	226 (46.7)	2,543 (51.6)	
	Large (> 1600)	146 (30.2)	1,160 (23.5)	0.005

Three covariates (farm type, production type and farm size, in bold) were included one at a time in the multivariate scanning statistics. A chi-square test was performed to test for significant differences in the prevalence of farms inside compared to outside the clusters.

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disease increases during winter and may explain some of the seasonal variation in antimicrobial use (Table 2).

Our aim was to identify persisting clusters regardless of seasonal variation. The seasonal variation in antimicrobial use (Table 2) supports the choice of study design where repeated spatial analyses were performed instead of a single spatio-temporal analysis. Clusters from the univariate and multivariate analyses were located in the same geographical areas, but did not entirely overlap. Unexpectedly, only 2% (1/51) of the farms with sows, and 63% (99/157) of the finisher farms were included in both a univariate and multivariate persistent cluster. One possible reason for the rest of the farms being omitted from the multivariate persistent cluster analysis could be a lower use of antimicrobials in the two other age groups.

In the repeated multivariate analysis, finishers seem to be the age group that influences clustering the most (Table 3), due to a difference of more than 104% in antimicrobial use inside versus outside the clusters. By comparison, antimicrobial use in weaners and sows differed by 19% and 4%, respectively. Data revealed that almost half the Danish farms (45.5%) hold more than one age group of pigs at the farm. Thus, comparing the total antimicrobial consumption between farms is ideally done using a multivariate analysis to determine consistency between all sections of antimicrobials consumed. The advantage of the multivariate cluster analysis is the inclusion of all three datasets, and consequently a higher study power [23].

Three covariates addressing farm characteristics (farm type, production type and farm size) were added to the multivariate analysis separately. All of the covariates reduced the size of significant persistent clusters and therefore seem to explain some of the persistent clustering. Firstly, farm type (nucleus /production) affected the degree of persistent clustering. Table 4 indicates a borderline significant higher proportion nucleus farms inside (5.3%) compared to outside (3.6%) the persistent clusters. The limited number of nucleus farms complicates identification of significance. However, nucleus sow farms may tend to produce high quality pigs with a lower threshold for initiating treatment. In agreement with this, Nielsen et al. [31] found SPF finisher farms to have three times higher treatment frequency than non-SPF farms.

Secondly, the covariate production type includes the presence of more age groups at the farm and is expected to affect the antimicrobial use directly, because a drug prescribed for one age group may in practice be used for another, as well as indirectly, because farms with more age groups are presumed to have more restrictions on the import of pigs and therefore pathogens. Farrow-to-finisher farms have been associated with a lower use of antimicrobials in prior studies [12,11], which might be explained by the lack of movement and mixing of pigs from various farms.

Thirdly, herd size seems to influence the clustering of antimicrobials. A significant difference was observed between the distribution of weaner and finisher farm sizes inside compared to outside the persistent clusters (Table 4). Additionally, adding herd size as predictor to the scanning statistics reduced the persistent clusters (Table 3).

Inclusion of information about the prescribing veterinarian was available in the data and would be of interest to explore. Veterinarians prescribe the drugs and guide the farmer in their correct usage, and are therefore expected to affect the overall use of antimicrobials at the farm to a large extent. Furthermore, veterinarians are expected to practice in certain geographic areas and might therefore explain some of the persistent clustering. However, the veterinarians form a hierarchical structure which cannot be included in the scan statistic analysis (at the current state of the methodology). The hierarchical structure is further complicated by the fact that farms may be associated with several veterinary clinics during the study period. Therefore, analysis incorporating the hierarchical structure was considered beyond the scope of the present study.

Results from this analysis indicate how multiple factors influence the use of antimicrobials for pigs. This study indicates that farm density, farm type, production type and farm size may explain some of the clustering of antimicrobial use. However, to quantify the effect of these factors, alternative study techniques are required.

Conclusion

This study revealed the presence of persistent clusters with higher levels of antimicrobials prescribed for finishers (157 farms), sows (51 farms) or all three age groups of pigs (551 farms). The persistent clusters were found in the same areas and overlapped to some extent. Production type, farm type and farm size all seemed to explain some of the persistent clustering in the multivariate cluster analysis, reducing the clusters by 24.3%, 30.5% and 34.1%, respectively.

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Author Contributions

Conceived and designed the experiments: MF JS AB NT. Performed the experiments: MF JS. Analyzed the data: MF JS AB HS ND NT. Contributed reagents/materials/analysis tools: MF ND. Wrote the paper: MF.

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4.3 Manuscript III

Changes in group treatment procedures and its influence on the amount of administered antimicrobials

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Changes in group treatment procedures of Danish finishers and its influence on the amount of administered antimicrobials

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When treating groups of pigs orally, antimicrobials can be administered through either feed or water. During the last decade, the group treatment procedure for finishers has shifted from feed to water administration. We hypothesized that farms implementing this change in treatment procedure would increase their total amount of administered antimicrobials. Based on Danish national register data, we performed a retrospective cohort study with three groups. The cohort of primary interest (Cohort Change) consisted of 50 finisher farms which changed their group treatment procedure from feed administration to water administration between 2008 and 2009. In addition, we identified 221 farms where treatment was administered through feed (Cohort Feed), and another 553 farms where treatment was administered through water (Cohort Water). Both of these groups retained their original treatment procedure throughout the study period. Cohort Change experienced a significant increase in the total amount of prescribed antimicrobials between the years. This increase might be caused by the treatment of more pigs, since antimicrobials administered through the feed are mainly administered at the pen level, while antimicrobials administered in water are mainly administered at the section level. However, we cannot exclude that a change in clinical disease has influenced the amount of prescribed antimicrobials. No change was observed in the other two cohorts. Furthermore, the difference in the amount of prescribed antimicrobials between the years was significantly different in Cohort Change when compared to both Cohort Water and Cohort Feed. Results from this study demonstrate that farms changing their procedure of group treatment from feed administration to water administration may increase their overall use of antimicrobials.

1. Introduction

In Denmark, treatment of production animals requires a veterinary prescription and is restricted to cases of clinical disease, excluding use for prophylaxis and growth promotion (Anon., 2014a). The majority of antimicrobial treatments for weaners and finishers are administered orally (Jensen et al., 2014), traditionally through group treatment. Group treatment accounts for 70% of all antimicrobials given to Danish finishers, calculated as ADDs. Group treatment may only be used for infectious conditions where a certain proportion of pigs in the pen or section are in a pre-clinical or clinical phase.

Antimicrobials used in group treatment can be categorized as water-soluble or non-water-soluble. The latter are mainly administered as top-dressing in dry-feed for the individual pen, whereas water-soluble antimicrobials are administered in wet-feed (through a medicine dispenser or directly in the trough) or in water (through a pipe or medicine dispenser) for the individual pen or section. The administration of antimicrobial treatment in water has two major advantages over administration in feed: (1) Feed intake is reduced in diseased pigs and therefore medicine intake is prone to under-dosage when administered in feed; (2) The drug mixes homogenously in water.

From 2005 to 2013, the amount of prescribed water-soluble antimicrobials increased from 33% to 59% of the total amount of antimicrobials (ADDs) prescribed for finishers. It has been speculated that administration of antimicrobials through water might result in the treatment of more animals. The objective of this study was to investigate how a change in the type of prescribed

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antimicrobials (water-soluble or non-water-soluble) affected the total quantity of prescribed antimicrobials.

2. Materials and methods

2.1. Study design

A retrospective cohort study with three cohorts was performed, based on three Danish national databases: Central Husbandry Register (CHR), Specific Pathogen Free register (SPF) and VetStat. On the basis of solubility of products prescribed for Danish pig farms as stated in VetStat, three cohorts were established. The cohort of primary interest included finisher farms that changed their antimicrobial group treatments from non-water-soluble to water-soluble products between 2008 and 2009 (Cohort Change). In addition, two cohorts of farms retaining their group treatment procedure from 2008 to 2009 were identified. These farms used either entirely water-soluble products (Cohort Water) or entirely non-water-soluble products (Cohort Feed).

2.2. Administration of antimicrobials

The quantity of prescribed antimicrobials was presumed to be a consistent proxy for the level of administered antimicrobials. Data on antimicrobials prescribed for pigs were retrieved from VetStat (Stege et al., 2003). All veterinary antimicrobial prescriptions for production animals are recorded in VetStat by feed mills, veterinarians and pharmacies. However, this study only included information from pharmacies, comprising more than 99% of the total amount of antimicrobials prescribed for pigs. To avoid disturbances of legislative actions, we chose to include data prior to July 2010 (Jensen et al., 2014; Anon., 2010).

To characterize prescribed antimicrobials as either water-soluble or non-water-soluble, we used the same classification as VetStat: “Based on the pharmaceutical formulation of the antimicrobial product, Vetstat uses the terminology given by the Health Authorities” (Erik Jacobsen, personal communication). Non-water-soluble substances (premixes and oral powders) were classified as being intended for feed administration, while water-soluble substances (soluble powders and oral solutions) were classified as being intended for water administration. All other formulations were characterized as being intended for single-animal treatments. Furthermore, the indication for prescription registered in VetStat was characterized as either (1) gastrointestinal disorders (2) respiratory disorders (3) joints/limbs/CNS (4) other (including urogenital, udder and generalized) disorders.

2.3. Study population

The selection procedure of farms for the three cohorts is illustrated in Fig. 1. Among all finisher farms, farms with changes in the number of registered finishers, production form or SPF-infection status[1] (Anon., 2015) during the study period were excluded. From the remaining farms, three cohorts were established:

- Cohort Feed: Farms that retained their procedure of group treatment administered 100% through feed between January 1st 2008 and December 31st 2009.
- Cohort Water: Farms that retained their procedure of group treatment administered 100% through water between January 1st 2008 and December 31st 2009.
- Cohort Change: Farms that changed their procedure of group treatment from 100% feed administration to 100% water administration. To retrieve a sufficient study population, three dates of transition were selected for this cohort: January 1st, April 1st and July 1st. This means that farms included in the first study period administered antimicrobials through feed from January 1st to December 31st 2008, and through water from January 1st to December 31st 2009, and likewise for the two other study periods. The total study period therefore ran from January 1st 2008 to June 30th 2010.

Data extractions from the CHR and SPF registers were from February 2008 (CHR and SPF), February 2009 (CHR and SPF) and October 2010 (CHR only).

2.4. Quantification of antimicrobials

Antimicrobials were quantified as Animal Daily Doses (ADDs) (Jensen et al., 2004). For comparison between farms, the amount of administered antimicrobials were aggregated at farm level and standardized as ADDs per 100 finishers per day, assuming an average weight of 50 kg at the time of treatment (ADD_{50}/100 finishers/day). This measure is in agreement with the official unit set by the Danish Veterinary and Food Administration (Anon., 2014b).

2.5. Statistical analysis

The difference in ADDs before and after the transition date (Cohort Change) or before and after 31 December 2008 (Cohort Feed and Cohort Water) was calculated for all farms in each of the three cohorts. This difference between years was used as the primary outcome in the statistical analyses. Non-parametric tests were performed due to non-normality in the outcome. A Kruskal–Wallis test was used to determine, whether there was a significant difference between years for all three cohorts and followed up by a pairwise comparison using a Tukey and Kramer test (Pohlert, 2015). Subsequently, a paired Wilcoxon signed-rank test was used to determine, whether the amount of antimicrobials was significantly different between years for each of the three cohorts. An ANOVA was used to test if the farm size differed significantly between the three cohorts. Likewise, a chi-square test was used to test for significant differences in prevalence of SPF-infection status and indication for prescription between cohorts.

Data management was carried out using the software SAS® (Statistical, 2014), while statistical analyses were performed in R (R Core Team, 2014).

3. Results

Extreme observations (37), crossing the first launched cut-off value of 8 ADD_{50}/100 finishers/day by the Danish Veterinary and Food Administration in 2010, were checked manually. In total, 37 farms administered more than 8 ADD_{50}/100 finishers/day, which was the limit for intervention from the Danish Veterinary and Food Administration in 2010 (Anon., 2010). Of these, 31 were from Cohort water, 5 were from Cohort Feed, and 1 was from Cohort Change. All 37 observations were checked manually, and none of these extreme values were due to changes in the number of registered pigs within the study period, so they were therefore retained in the final dataset.

The resulting dataset held 50 farms in Cohort Change, 221 farms in Cohort Feed and 553 farms in Cohort Water. A significant increase in the amount of antimicrobials administered between 2008 and

[1] SPF pathogens include the following: Porcine Reproductive- and Respiratory Syndrome European variant (PRRS-DK) and American/Vaccine variant (PRRS-Vac), *Actinobacillus pleuropneumoniae* (App) serotype 1–12 (except serotype 11), *Mycoplasma hyopneumoniae* (Myc), *Brachyspira hyodysenteriae* (Dys), toxin-producing *Pasteurella multocida* (Nys).

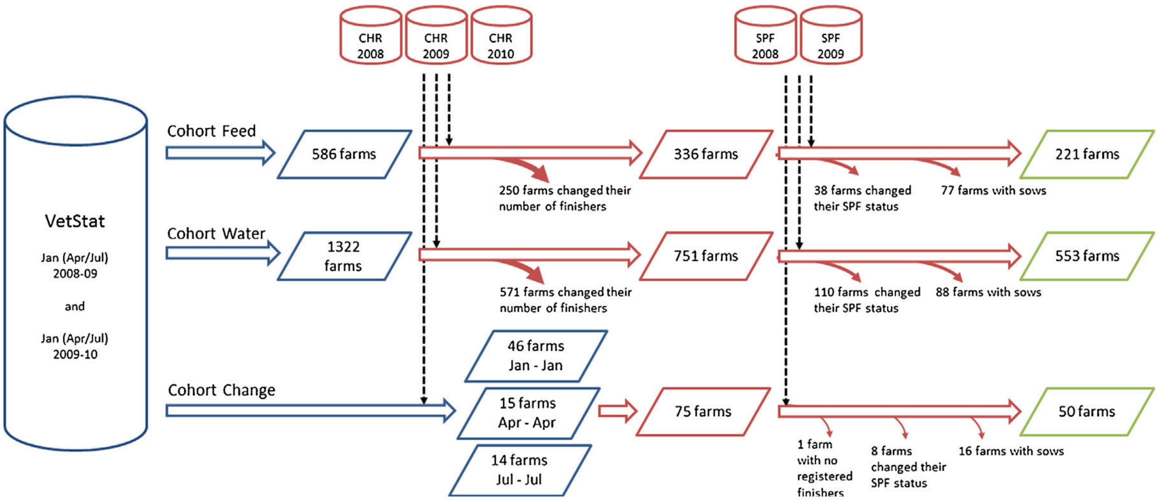

Fig. 1. Flow diagram of the selection process for three cohorts of Danish finisher farms, based on their group treatment procedure. Cohort Feed and Cohort Water both retained their procedure of antimicrobial group treatment through either feed administration or water administration during 2008–09, respectively. Cohort Change altered their method of treatment from feed administration (2008) to water administration (2009). Data on antimicrobials used for finishers were extracted from VetStat. Data from CHR and SPF were merged to exclude farms with changes in farm size and/or SPF status. Colors indicate the inclusion (blue) and exclusion (red) process, as well as the final (green) dataset. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Farm characteristics of three cohorts of Danish finisher farms, either changing (Cohort Change) or retaining (Cohort Feed and Water) their group treatment procedure in 2008–09**.** Number of farms in each cohort, number of finishers and the prevalence of farms non-SPF and SPF farms (with associated relevant pathogens) are presented.

		Cohort Change	Cohort Feed	Cohort Water	*p*-value
No. of farms		50	221	553	
No. of finishers (median [IQR])		1075 [712;1750]	1200 [800;1725]	1350 [900;1900]	0.080
Non-SPF farms		40 (0.80)	150 (0.67)	431 (0.78)	0.010
SPF farms		10 (0.20)	71 (0.32)	122 (0.22)	
	Myc	8 (0.80)	51 (0.72)	92 (0.75)	0.788
	App2	3 (0.30)	8 (0.11)	19 (0.16)	0.273
	App6	4 (0.40)	29 (0.41)	45 (0.37)	0.857
	App12	7 (0.70)	52 (0.73)	81 (0.66)	0.610
	PPRS-DK	6 (0.60)	20 (0.28)	54 (0.44)	0.034
	PRRS-Vac	5 (0.50)	19 (0.27)	28 (0.23)	0.163

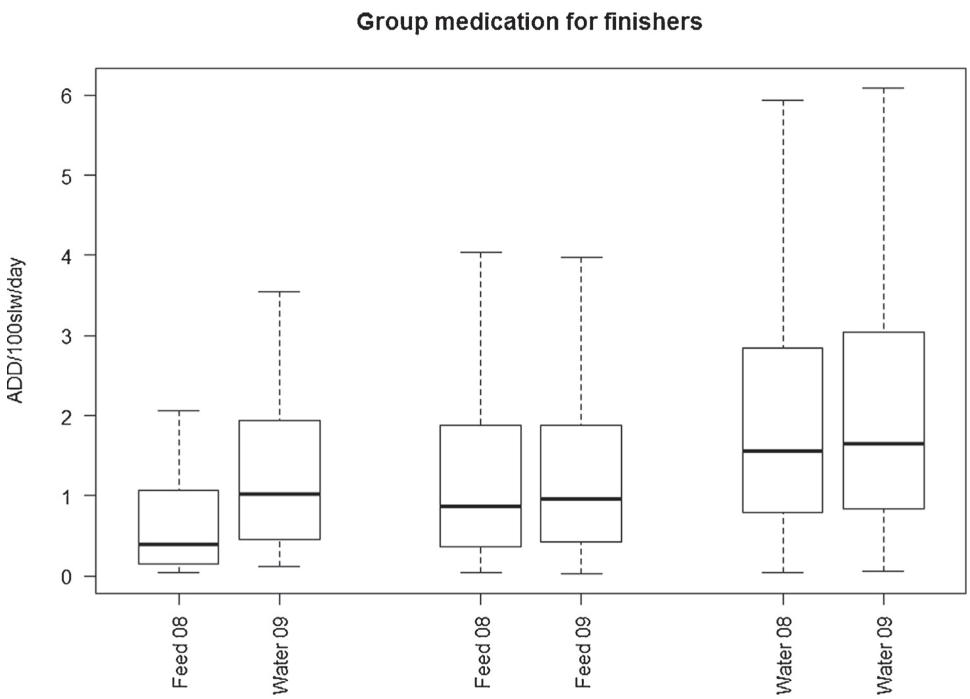

Fig. 2. Boxplots illustrating the use of antimicrobials in three paired cohorts of Danish finisher farms, selected based on their group treatment procedure. Group 1 (Cohort Change; 50 farms), changed their antimicrobial group treatment procedure from feed administration (2008) to water administration (2009). Between 2008 and 2009, Group 2 (Cohort Feed; 221 farms) and Group 3 (Cohort Water; 553 farms) both retained their method of antimicrobial group treatment through either feed or water, respectively. Outliers (defined as more than 1.5 times the range above the third quartile) are not illustrated but are included in the analysis.

Table 2
Total amount of prescribed antimicrobials measured as Animal Daily Doses per 100 finishers per day (ADD/100 finishers/day) in three cohorts of Danish finisher farms, either changing (Cohort Change) or retaining (Cohort Feed and Water) their treatment procedure in 2008–09.

Treatment procedure	ADD Median	ADD [IQR]	*P*-value
Cohort Change ($n = 50$)			
2008 (feed)	0.40	[0.15;1.06]	<0.001
2009 (water)	1.03	[0.47;1.88]	
Cohort Feed ($n = 221$)			
2008 (feed)	0.87	[0.36;1.87]	0.119
2009 (feed)	0.96	[0.42;1.87]	
Cohort Water ($n = 553$)			
2008 (water)	1.56	[0.79;2.85]	0.102
2009 (water)	1.65	[0.84;3.04]	

2009 was observed in Cohort Change. No significant increase was found in the other two cohorts (Table 2 and Fig. 2). There was a significant difference in the amount of antimicrobials between Cohort Change 2008 and Cohort Feed 2008 ($p < 0.001$) and between Cohort Change 2009 and Cohort Water 2009 ($p < 0.001$), but no difference between Cohort Change 2009 and Cohort Feed 2009 ($p = 0.723$).

The difference in quantity of prescribed antimicrobials from 2008 to 2009 was significantly different between the three cohorts (p-value = 0.015). Post hoc pairwise tests found a significant difference between Cohort Change and Cohort Feed (p-value = 0.012) and between Cohort Change and Cohort Water (p-value = 0.018). No difference was found between Cohort Feed and Cohort Water (p-value = 0.841). Indications for which antimicrobials were prescribed remained stable for both Cohort Feed and Cohort Water during 2008–2009. For both cohorts, around two thirds of antimicrobials were prescribed for gastrointestinal disorders, while Cohort Water received a slightly higher amount of antimicrobials for respiratory disorders (23–25%), compared to Cohort Feed (13–16%). In general, Cohort Change received more antimicrobials for joints/limbs/CNS disorders (29–31%) compared to both control cohorts (16–20%). Likewise, Cohort Change increased the usage of antimicrobials for respiratory disorders from 8% in 2008 to 16% in 2009, at the expense of antimicrobials for gastrointestinal disorders.

Recommended length of treatment did not differ significantly between products for feed- and water treatments. Of the four products most commonly prescribed for group medication in water or feed, the recommended length of treatment were in the interval of 3–6 days and 5–7 days, respectively (Anon., 2016).

In the data describing the investigated farms, there were no statistical difference in farm size, while the proportion of SPF farms differed between the three cohorts ($p = 0.010$), and among SPF farms, PRRS-DK was the only SPF pathogen, where the prevalence differed significantly ($p = 0.034$) (Table 1).

4. Discussion

This study demonstrated a significant increase in the total amount of antimicrobials prescribed for finisher farms, when there was a change from non-water-soluble to water-soluble treatments. A similar change was not seen in farms, which retained their group treatment procedure. Antimicrobials added to feed are often administered at pen level, while antimicrobials added to water are typically administered at section level. Therefore, this change in administration procedure can be expected to lead to an increased number of treated pigs and therefore a larger amount of prescribed antimicrobials.

Unexpectedly, the amount of antimicrobials used was significantly smaller in Cohort Change 2008 compared to Cohort Feed 2008 (Fig. 2). This might be explained by a lower frequency of respiratory disorders as observed in the prescription pattern. From 2008 to 2009, the proportion of antimicrobials prescribed for respiratory disorders increase from 8% to 16% in Cohort Change reaching the proportion as Cohort Feed. Simultaneously, the antimicrobial usage of Cohort Change increased to the level of Cohort Feed. Opposite, Cohort Water had a significantly higher antimicrobial usage as well as a higher proportion of antimicrobials for respiratory disorders. Thus, we cannot exclude that the level of respiratory diseases may have affected the amount of antimicrobials used in Cohort Change. An alternative explanation could be that farms changing their procedure of group treatment simply are characterized by having an initially low usage of antimicrobials.

In reality Cohort Water consists of farms treating in water and farms treating in wet-feed. No Danish register holds information on the type of feeding, and it was therefore not possible to divide water treatments into these two groups. In principle, farms in Cohort Change could have changed feeding procedure, from dry- to wet-feed, instead of treatment procedure, from feed- to water. However, both dry feed and wet feed administered antimicrobials are usually administered at the pen-level. Therefore, we would not expect such a change to lead to changes in the amount of prescribed antimicrobials.

When recommended times of treatment were compared to the prescribed types of antimicrobials, there were no indications that the increased amounts could be caused by changes to types of antimicrobials with longer treatment times.

According to the registers, the only changes experienced by the farms included in the study population were related to the treatment procedures, meaning that there were no changes in farm size or infection status. However, since this study is based purely on register data, we do not have any information on management practices or changes in management. Furthermore, we do not have any information on the disease status in the farms, with the exception of those farms and diseases included in the SPF register.

In Denmark, the majority of antimicrobials for oral use (and thus for group treatments) are administered for weaners (Jensen et al., 2014), and it would have been optimal to investigate antimicrobial use in this population. However, the number of weaners was not originally registered in CHR, making the number of registered finishers a more reliable measure.

5. Conclusion

This study demonstrated that a change in group treatment procedure from feed to water administration resulted in a significantly higher use of antimicrobials. However, we cannot exclude that changes in occurrence of clinical disease may have influenced the findings. The findings of this study indicate that when considering the total use of antimicrobials in intensive pig production, more attention should be given to group treatment and the methods of drug delivery.

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4.4 Manuscript IV

A register-based study of antimicrobial usage in Danish veal calves and young bulls

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A register-based study of the antimicrobial usage in Danish veal calves and young bulls

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ABSTRACT

High antimicrobial usage and multidrug resistance have been reported in veal calves in Europe. This may be attributed to a high risk of disease as veal calves are often purchased from numerous dairy herds, exposed to stress related to the transport and commingling of new animals, and fed a new ration. In this study, we used national register data to characterize the use of antimicrobials registered for large Danish veal calf and young bull producing herds in 2014.

A total of 325 herds with veal calf and potentially young bull production were identified from the Danish Cattle database. According to the national Danish database on drugs for veterinary use (VetStat), a total of 537,399 Animal Daily Doses (ADD_{200}) were registered for these 325 herds during 2014. The amount of antimicrobials registered in 2014 varied throughout the year, with the highest amounts registered in autumn and winter. Antimicrobials were registered for respiratory disorders (79%), joints/limbs/CNS disorders (17%), gastrointestinal disorders (3.7%) and other disorders (0.3%). Of the registered antimicrobials, 15% were for oral and 85% for parenteral administration. Long-acting formulations with a therapeutic effect of more than 48 h covered 58% of the drugs for parenteral use. Standardized at the herd-level, as ADD_{200}/100 calves/day, antimicrobial use distributed as median [$CI_{95\%}$] for starter herds (n = 22): 2.14 [0.19;7.58], finisher herds (n = 24): 0.48 [0.00;1.48], full-line herds (n = 183): 0.78 [0.05;2.20] and herds with an inconsistent pattern of movements (n = 96): 0.62 [0.00;2.24]. Full-line herds are herds, which purchase calves directly from a dairy herd and raise them to slaughter.

Furthermore, we performed a risk factor analysis on the 183 herds with a full-line production. Here, we investigated, whether the number of suppliers, the number of calves purchased, the frequency of purchase, the average age at introduction, the average time in the herd and vaccination influenced the amount of antimicrobials used in the herds. The final multivariable regression analysis revealed that the number of calves introduced was positively associated with the antimicrobial use in the herd.

1. Introduction

High antimicrobial usage and multidrug resistance have been found in Belgian and Dutch veal calves (Catry et al., 2007; Pardon et al., 2012a; Bos et al., 2012). In the same countries antimicrobial usage in veal calves has been found to exceed that of pig, poultry, dairy and beef cattle production (Pardon et al., 2012a; Bondt et al., 2013). An explanation may be that producers of pigs and poultry receive animals from a limited number of suppliers, while veal calf producers typically purchase calves from numerous dairy herds. A large number of suppliers, new feed and stress related to the transport and commingling of new animals exposes veal calves to a high risk of disease and may explain the higher use of antimicrobials (Pardon et al., 2012a).

Veal calf production can generally be divided into two types; white and rosé veal calf production. White veal calves are primarily fed on calf milk replacer and are slaughtered at around 6–8 months of age, while rosé veal calves are weaned in the beginning of the fattening period and subsequently fed on roughage and concentrate, until they are slaughtered at around 8–12 months of age (Bos et al., 2012). Additionally, rosé veal calf production can be divided into rosé starter and rosé finisher herds with large differences in antimicrobial usage (Bos et al., 2013).

Denmark only produce rosé veal calves. The vast majority of Danish rosé veal calves, are bull calves purchased from domestic dairy herds. Some of the calves are slaughtered as veal (8–12 months of age) (EU Regulation EC, 2007), while some are slaughtered as young bulls (>12 months of age) (Danish Agriculture and

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Food Council, 2016). In 2014, around 200,000 veal and young bulls were slaughtered in Denmark (Danish Agriculture and Food Council, 2015). Heifers only make up around 1% of the total number of produced calves (SEGES, 2016). After arrival in a specialized veal calf herd, the calves receive calf milk replacer until around 8 weeks of age, after which they are typically fed on a ration of grain and concentrate or on a total mixed ration based on corn silage. The calves are predominantly Danish Holsteins, though a small percentage of them are Holstein crossbreds. Specialized Danish rosé veal calf producers generally keep the calves in compartments of multiple straw-bedded pens or cubicles, where each unit may hold 6–50 calves of the same age, depending on the producer. Typically, an all-in-all-out production is implemented at pen level, but not at compartment level. Depending on the facilities, this may result in calves of different ages being housed under the same roof, thus facilitating the transmission of airborne pathogens (Mars et al., 1999; Niskanen and Lindberg, 2003).

In herds with a Veterinary Advisory Service Contract, Danish veterinarians can prescribe drugs for use within 63 days (Anon., 2016). This means that most Danish veal and young bull producers have a veterinary visit at least every second month. All prescription-only drugs for veterinary use are registered in the national database VetStat, which holds detailed information on each purchase of drug such as the date, prescribing veterinarian, receiving herd ID, species, age group and clinical indication (Stege et al., 2003). In addition, the Danish cattle database holds detailed information on all Danish cattle and their movements, including the date of birth, date of movement and herd ID of the sender and recipient.

There is limited research into the overall disease occurrence in Danish veal calf production. A study from 1984 found pneumonia and enteritis to be the predominant diseases (Madsen, 1984). In Swiss and Belgian white veal calves, respiratory disease was found to be the main indication for antimicrobial treatment (Pardon et al., 2012a; Lava et al., 2016b), with a peak incidence in the third week after arrival (Pardon et al., 2012b). The second most common indication for treatment of Belgian white veal calves was diarrhea (12%), while arrival prophylaxis made up 13% of the treatments (Pardon et al., 2012a). Group treatments were widely applied in the production in both countries (>84%) (Pardon et al., 2012a; Lava et al., 2016b).

Recent risk factor studies on white veal calves in Switzerland have demonstrated purchase of calves and herd size to be significantly associated with the use of metaphylactic treatments (Lava et al., 2016a), while the lack of quarantine and clinical examination upon arrival, as well as shared airspace for several groups of calves were associated with an increased antimicrobial usage (Lava et al., 2016b). To the best knowledge of the authors, no risk factor study on rosé veal calf production has so far been carried out. Therefore, based on register data, our aim was to characterize antimicrobial usage in Danish veal calves specified in the following two objectives:

a Describe the total amount of antimicrobials registered for all large Danish herds with a veal calf and potentially young bull production in 2014.
b Identify risk factors influencing the amount of antimicrobials registered at herd level in large Danish herds which purchased calves and raised them to slaughter (full-line production).

2. Materials and methods

2.1. Study population

Based on the Danish Cattle database, herds included in the study population had to fulfill the following three criteria:

1. No delivery of milk to a dairy in 2014
2. Slaughter more than 100 bull calves in 2014
3. Less than 80% of the cattle in the herd should be of dairy or mixed breeds

Bovines which had stayed in one of the study herds in the period 01 January, 2014–31 December, 2014 were included. For these animals, all movements were extracted from the Danish Cattle database until 31 December 2014. Based on the definition of veal by the European Council (EU Regulation EC, 2007), calves were defined as being less than 366 days of age at the time of slaughter. Only bovines which were calves (<366 days of age) at the time of introduction in one of the study herds were retained in the final dataset.

For each calf, we consecutively numerated each herd through which the calf had passed, aside from the originating dairy herd, markets and delivering traders. Based on this, we defined four different types of herds: Starter and full-line herds, where ≥95% of the calves entering the herd came directly from the herd where they were born (possibly through a market or delivery trader); and finisher herds, where ≥95% of the entering calves came from a starter herd. Herds with a low average age of exit (<250 days) or a high variance in the age at exit (>10 days) were checked manually, to differentiate starter and full-line herds. Herds, which did not fulfill the definitions of starter, finisher or full-line herds, were defined as herds with inconsistencies in movements.

The number of registered calves on the first day of each month was extracted from the Danish Cattle database. We calculated a weighted herd size for 2014 based on this information and taking into account the number of days in each month. Additionally, calf mortality from day 0–180 was calculated for each herd as a modified Kaplan-Meier estimate. The Kaplan-Meier estimate follows a specific cohort of calves during the first 180 days of their lives, for which a mortality risk is calculated as the number of fallen and euthanized calves divided by the number of calves at risk (Nielsen et al., 2010). Due to availability of data, the calf mortality was stated for the period between 01 October, 2014 and 30 September, 2015, covering calves born between 01 April, 2014 and 31 March, 2015. For each herd, we summarized the number of calves purchased, the average age at introduction, the average time in the herd, frequency of purchase, purchase from markets and delivering traders, and the number of suppliers (excluding delivering traders and markets). Furthermore, we calculated the proportion of calves slaughtered <366 days of age out of the total number of slaughtered bovine.

2.2. Antimicrobial prescriptions

In VetStat, all prescription-only drugs for production animals are registered in detail at the time of purchase by farmers (from either pharmacies or veterinarians) (Stege et al., 2003). We retrieved records on antimicrobials for calves registered by both pharmacies and veterinarians in 2014 from VetStat on 01 June, 2015. Antimicrobials registered by veterinarians were manually checked and systematic errors were corrected. Furthermore, registrations with an invalid code of indication (e.g. disease in other species) were deleted.

For each herd in the study, the amount of antimicrobials registered in VetStat for calves was used as a measure for the amount of antimicrobials used. Antimicrobials were quantified as the number of Animal Daily Doses (ADD_{200}) (Jensen et al., 2004). Based on the official Danish quantification of antimicrobials, we used a standard weight of 200 kg for calves (personal communication Erik Jacobsen, Danish Veterinary and Food Administration). The standard dose, ADD_{200} corresponds to the treatment of one 200 kg calf for one day. For comparison between herds, the amount of antimicrobials was standardized in agreement with the official unit as the number of Animal Daily Doses per 100 calves per day (ADD_{200}/100 calves/day). This unit approximates the percentage of calves treated daily at the herd assuming that all calves weigh 200 kg (Anon., 2014). Based on the Anatomical Therapeutic Chemical classification system, antimicrobial products were grouped according to active substance as amphenicols, combination products (all except sulphonamide/trimethoprim and lincospectin), macrolides, sulphonamide/trimethoprim, tetracyclines, simple or extended-spectrum penicillin products, lincospectin, lincosamides, cephalosporin, aminoglycosides and colistin. The products were further characterized as intended for parenteral or oral use, based on the definitions in VetStat. Clinical indication according to diagnostic grouping in VetStat (Stege et al., 2003) was categorized as gastrointestinal, respiratory, joint/limbs/Central Nervous System (CNS) or other disorders (covering the three VetStat diagnostic groups reproduction, udder and metabolism as well as missing disorders). In addition, information about registered vaccines against respiratory disorders was extracted.

2.3. Statistical analyses

For all large Danish herds producing veal calves and young bulls, a descriptive analysis was performed, including the total amount of antimicrobials registered, quantified as ADD_{200}, according to months of registration, route of administration, antimicrobial active substance and clinical indication, as stated in VetStat.

For full-line herds, we performed a multivariable regression analysis with ADD_{200}/100 calves/day as the response variable. Potential risk factors included: Herd size, number of suppliers, number of calves purchased, frequency of purchase, average age at introduction, average time in the herd and vaccination.

The number of calves introduced was 10 log-transformed to improve linearity with the outcome. Additional continuous risk factors with a non-linear relationship with the outcome were each categorized into three categories according to their distribution. Prior to categorization, the correlation between all continuous explanatory variables were investigated two at a time, and if Spearman's coefficient >0.6 only one of the parameters was included in the final model.

Initially, each possible risk factor was tested with the outcome in a univariable analysis. If found to be significant ($p < 0.05$), pairwise post-test comparisons were performed using the contrast procedure in the Least-Squares Means package in R (Lenth and Herv, 2015). For the multivariable analysis, all factors sufficiently associated with the outcome ($p < 0.20$ in univariable analysis) were included. All biologically plausible interactions were assessed individually to see, if they significantly improved the model including all risk factors. Following this, the model with all risk factors was reduced by stepwise backward elimination. To improve the residuals of the model, the outcome was Box-Cox transformed. Due to null-values, we added half the minimum value to the outcome prior to the Box-Cox transformation.

Data management was carried out using the software SAS® (SAS Institute Inc., 2014), while statistical analyses were performed in R (R Core Team, 2014).

3. Results

3.1. Descriptive analyses of the study population

A total of 333 herds fulfilled the initial inclusion criteria. Subsequently, 8 herds were excluded due to cessation (1), systematic incorrect registrations (1), partly beef production (2) and combined starter-/full-line production (4).

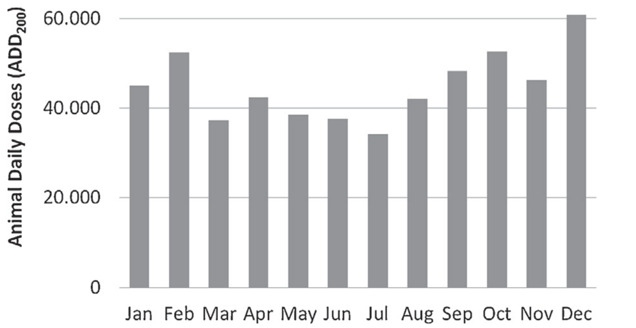

Fig. 1. Variation in the amount of registered antimicrobials in 2014 for 325 Danish herds producing veal calves and young bulls. Antimicrobials are quantified as Animal Daily Doses for calves (ADD_{200}), illustrated according to the month of prescription.

Of the cattle present in the remaining 325 herds, 242,474 (98.7%) of them had entered one/more study herds as calves <366 days of age and 3224 (1.3%) as bovine ≥366 days of age. The latter category of cattle was excluded from further analysis. Of the 242,474 calves entering, 176,897 (73.0%) were slaughtered as veal (<366 days) with a median slaughter age at 300 days, $CI_{95\%}$ [271;354], while 43,780 (18.1%) were slaughtered as young bulls (≥366 days), with a median slaughter age of 403 days, $CI_{95\%}$ [369;814] at the time of slaughter. The remaining 21,797 (9.0%) calves were not slaughtered prior to 01 January, 2015.

Based on the movement of calves, we defined 22 starter herds, 24 finisher herds, 183 full-line herds and 96 herds with inconsistent movements of calves. Herds with inconsistencies in movements received calves by the second to seventh movement of the calf after it left the dairy herd (average 2.3 movements).

The majority of starter-, finisher and full-line herds slaughtered more than 90% of their calves as veal <366 days of age, while herds with inconsistent movements slaughtered a larger proportion of young bulls ≥366 days (Table 1).

In total, twelve herds purchased calves from delivering traders and 19 herds purchased from markets. From these sources, the herds received a median number of six calves (ranging from 1 to 398) and nine calves (ranging from 1 to 269), respectively.

3.2. Descriptive analyses of antimicrobials registered for all large Danish herds producing veal calves and young bulls

In 2014, a total of 1,062,376 ADD_{200} were registered for calves in VetStat. Of these, 537,399 ADD_{200} (51%) were registered for the selected 325 large veal calf and young bull producing herds, with 532,438 ADD_{200} (99%) originating from pharmacies and 4961 ADD_{200} (1%) from veterinarians.

The amount of antimicrobials varied between seasons, with the largest amounts of antimicrobials registered in autumn and winter (September–February) (Fig. 1).

Of the registered antimicrobials, 85.4% were for parenteral use and 14.6% for oral use. Long-acting formulations with a therapeutic effect of more than 48 h covered 58% of all antimicrobials for parenteral use. Amphenicols, macrolides and extended penicillins were the primary active substances of long-acting formulations. For oral use, the majority of antimicrobials were soluble tetracyclines (Fig. 2). Lincospectin, lincosamide, cephalosporin, aminoglycoside and colistin only covered a total of 1603 (0.3%) ADD_{200} and are therefore not illustrated in Fig. 2.

Respiratory disorders were the primary indication for antimicrobial use, accounting for 78.9% of all ADD_{200} in 2014. Joints/limbs/CNS disorders accounted for 17.1%, gastrointestinal disorders for 3.7% and other conditions for 0.3% of the total amount of ADD_{200} (Fig. 2).

Table 1
Characteristics of 325 Danish herds producing veal calves and young bulls in 2014. Herds are characterized according to their type of production as either starter, finisher, full-line or herds with inconsistent movements. Values are presented as the median and 95% confidence interval.

	Starter	Finisher	Full-line	Inconsistent
Number of herds	22	24	183	96
Number of introduced calves[a]	1597 [445;3764]	512 [186;2074]	474 [203;2533]	524 [226;2349]
Proportion of veal calves produced[b]	0.97 [0.32;0.99]	0.97 [0.12;1.00]	0.94 [0.18;1.00]	0.60 [0.21;0.99]
Number of purchases (in 2014)[c]	71 [25;169]	21 [7;35]	53 [18;115]	63 [19;135]
Number of suppliers[d]	27 [6;65]	1 [1;7]	8 [1;70]	14 [2;75]
Average age at introduction (days)	32 [27;44]	151 [100;266]	32 [19;98]	NA
Average length of time in herd (days)	172 [97;210]	166 [112;276]	263 [220;374]	257 [94;483]
Number of herds using vaccines	3	0	17	5
Mortality day 0–180 (%)[e]	4.2 [0.00;10.0]	0.0 [0.0;10.3]	3.7 [0.2;11.8]	4.0 [0.0;19.0]

[a] Total number of introduced calves during 2014.
[b] Of the number of calves passing through the herd, the proportion of veal calves has been calculated as the number of calves slaughtered as veal (<366 days of age) divided by the number of cattle slaughtered (≥366 days of age) (which entered the herd as calves).
[c] Frequency of purchase is defined as the number of days during 2014, where the herd received calves.
[d] Seven full-line herds had more than one supplier.
[e] Information on mortality was not available for 52 herds, covering three starter, eight finisher, 16 full-line and 24 herds with inconsistent movements.

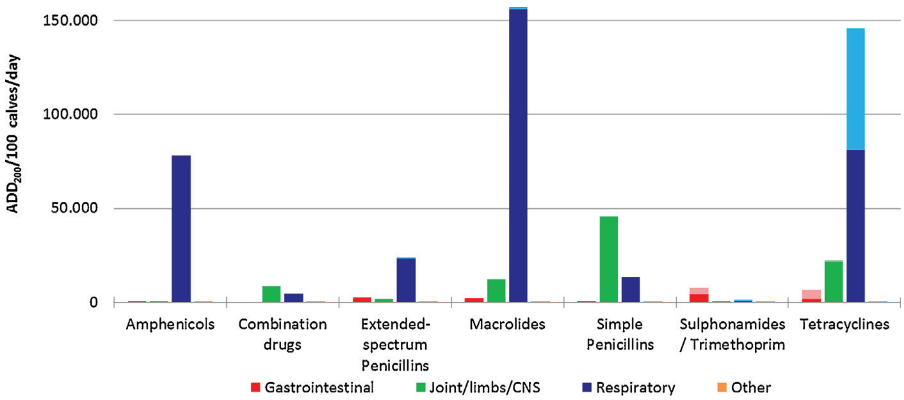

Fig. 2. Antimicrobials according to active substance and clinical indication registered for use in 325 Danish herds producing veal calves and young bulls in 2014. The total amount of the seven most registered antimicrobial active substances. Antimicrobials are quantified as Animal Daily Doses for a calf (ADD_{200}). Dark colors indicate parenteral and light colors oral administration. Combination drugs all include Penicillin-combination drugs.

Antimicrobials registered for respiratory disorders primarily included macrolides (37%) and tetracyclines (34%), while simple penicillins (50%) were most often registered for joints/limbs/CNS disorders, and sulphonamides/trimethoprim (39%) and tetracyclines (33%) for gastrointestinal disorders.

Standardized at the herd-level, antimicrobial use, measured as ADD_{200}/100 calves/day, distributed as follows (median [$CI_{95\%}$]) for starter herds (n = 22): 2.14 [0.19;7.58], for finisher herds (n = 24): 0.48 [0.00;1.48], for full-line herds (n = 183): 0.78 [0.05;2.20] and for herds with an inconsistent pattern of movements (n = 96): 0.62 [0.00;2.24]. Starter herds used significantly more antimicrobials than all other herd types ($p < 0.001$), while no difference was demonstrated in antimicrobial usage between any of the other production types (Fig. 3).

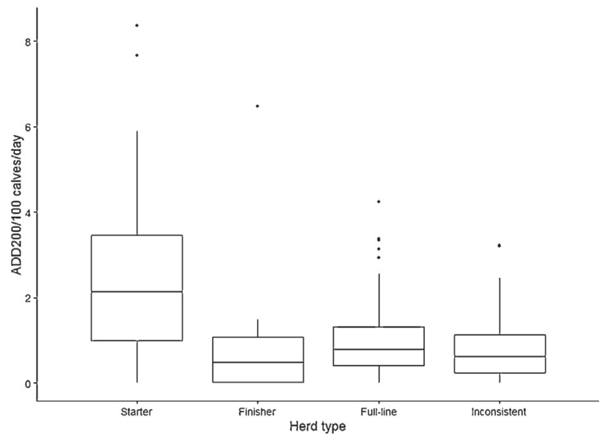

Fig. 3. Antimicrobials registered in relation to herd type in 325 Danish herds producing veal calves and young bulls. Antimicrobials are quantified as Animal Daily Doses (ADD_{200}) per 100 calves per day.

3.3. Risk factors for use of antimicrobials in large Danish full-line herds producing veal calves and young bulls

Of the previously described 325 herds, 183 had a full-line production and were included in the risk-factor analysis. Of these herds, 6 (3%) had not purchased antimicrobials in 2014.

Several of the investigated risk factors were correlated, and therefore not all factors could be included in the model. The number of suppliers was positively correlated with the herd size (Spearman's coeff = 0.67) and the number of inserted calves (Spearman's coeff = 0.69), like herd size was correlated with the number of inserted calves (Spearman's coeff = 0.98). We kept the number of inserted calves in the model, since we found this to be the most valid parameter of the investigated parameters.

In the univariable analyses, antimicrobial usage was significantly higher in herds with a short average length in the herd (<291 days), large number of purchases per year (>61) or a large number of introduced calves. Herds which introduced calves at a low (12–28 days) or high (35–240 days) age had a significantly lower use of antimicrobials than herds where calves were introduced at a medium (39–34 days) age. Herds introducing young calves kept the calves significantly longer time in the herd, compared to herds which introduced calves older than 29 days of age

Table 2
Univariable comparisons of risk factors for the amount of registered antimicrobials in 183 Danish herds producing veal calves and young bulls in 2014. Antimicrobials are standardized at the herd level as Animal Daily Doses (ADD_{200}) per 100 calves per day.

Potential categorical risk factors	Number of herds (%)	ADD_{200}/100 calves/day median [$CI_{95\%}$]	p-value[a]
Average age at introduction (days)			<0.001
12–28	62 (34)	0.73 [0.15;1.73][a]	
29–34	48 (26)	1.27 [0.32;2.30]	
35–240	73 (40)	0.60 [0.00;2.09][a]	
Average length of time in herd (days)			<0.001
131–255	56 (31)	1.10 [0.00;3.19][a]	
256–290	61 (33)	0.86 [0.21;2.14][a]	
291–641	66 (36)	0.47 [0.06;1.31]	
Number of purchases (in 2014)			0.004
7–45	65 (36)	0.59 [0.00;2.01][a]	
46–60	52 (28)	0.60 [0.19;2.14][a]	
61–233	66 (36)	0.96 [0.18;2.49]	
Purchase of calves from markets or delivering traders			0.980
–	174 (95)	0.78 [0.05;2.24]	
+	9 (5)	0.83 [0.29;1.67]	
Vaccination			0.927
–	166 (91)	0.77 [0.05;2.26]	
+	17 (9)	0.83 [0.28;1.97]	
Potential continuous risk factors	Estimate	SE	
Log_{10} (Calves introduced)	1.52	0.13	<0.001

[a] For categorical variables, a *t*-test or ANOVA was performed on the Box-Cox transformed outcome ((ADD_{200}/100 calves/day + 0.00275)$^{0.424}$). Superscripts of lower case letters indicate non-significance in the antimicrobial usage between strata of the given variable. For the continuous variable, the result from the univariable linear regression on a non-transformed outcome is presented.

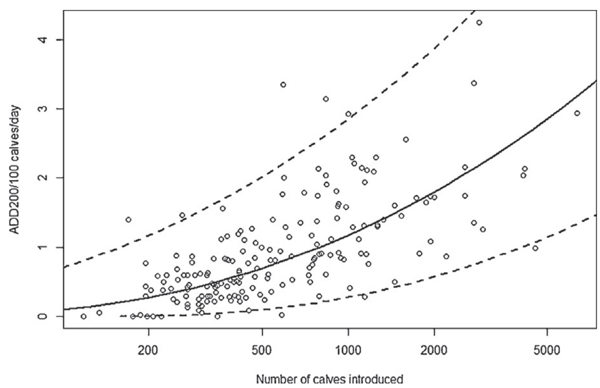

Fig. 4. Prediction lines for the antimicrobial usage based on the number of introduced calves in 183 Danish full-line herds producing veal and young bulls. Prediction lines are estimated based on a linear regression analysis with the number of introduced calves as only significant risk factor for antimicrobial usage in Danish veal calf herds. The x-axis is on the log-scale.

($p = 0.037$). No effect was demonstrated from purchase from markets/delivering traders or vaccination (Table 2). Only one vaccine was used against respiratory disorders. This was a combination vaccine holding inactivated bovine respiratory syncytial virus (BRSV), parainfluenza-3-virus (PI-3) and *Mannheimia haemolytica* serotype A1.

The initial regression analysis included average age at introduction, average length of time in the herd, frequency of purchase, vaccination, breeding of own calves and number of calves introduced. The final model had (ADD_{200}/100 calves/day + 0.00275)$^{0.424}$ as outcome and log10(number of introduced calves) as only significant risk factor ($p < 0.001$) with an intercept of −1.04 (SE = 0.16) and an estimate of 0.70 (SE = 0.06). The predicted antimicrobial use (back-transformed) as a function of the number of introduced calves is presented in Fig. 4.

4. Discussion

Antimicrobials registered for the selected 325 large veal calf and young bull producing herds, covered 51% of the total amount of antimicrobials registered for calves in Denmark. The majority of antimicrobials (78.9%) were registered for respiratory disease. This is in line with previous studies showing bovine respiratory disease to be the clinical indication of 56.1% (Pardon et al., 2012b) to 73% (Lava et al., 2016b) of the antimicrobial treatments. Penicillin is the recommended first drug of choice for respiratory diseases (SEGES Dairy and Beef Research Centre et al., 2013), yet, in our study, this accounted for only 9% of the antimicrobials registered for respiratory disorders (Fig. 2). Incongruence between recommendations and use may be due to tradition, unawareness or a lack of clinical effect.

The second largest amount of antimicrobials was registered for joints/limbs/CNS disorders (17.1%). This VetStat category includes a number of various disorders which clinically are not related, e.g. omphalitis, arthritis, otitis media and interdigital phlegmon. Based on VetStat registrations, it is not possible to specify which clinical conditions registered drugs are supposed to target. Arthritis is more prevalent in young calves, while interdigital phlegmon typically is seen in older calves >240 days of age. Hence, a large amount of antimicrobials may be used for the latter, but only cover a relatively small number of treatments due to the treatment of heavier cattle (Ortman and Svensson, 2004). Pardon et al. (2013) found otitis and arthritis to represent 1.5% and 1.6% of the initial causes of antimicrobial treatment, which can be explained by a high prevalence of *Mycoplasma bovis*. *M. bovis* is highly prevalent among veal calves in Europe (Arcangioli et al., 2008; Radaelli et al., 2008; Pardon et al., 2013) and North America (Soehnlen et al., 2012). Recently, *M. bovis* has also been found in Danish veal calf herds (Nielsen, 2016) and may be responsible for a proportion of the treatments of joints/limbs/CNS and respiratory disorders in young calves. Mycoplasmas are innate resistant to penicillin (Taylor-Robinson and Bébéar, 1997), which may explain the relatively low use of penicillin (Fig. 2).

Although injection of antimicrobials requires a higher workload, more on-farm awareness and well-educated staff (Pardon et al., 2012a) compared to peroral administration, the vast majority of antimicrobials used in Danish veal calves and young bulls were administered parenterally (85.4%). Only 14.6% were administered orally, in contrast to white veal calf production in Switzerland (84.6%) (Lava et al., 2016b) and Belgium (95.8%) (Pardon et al., 2012a). An explanation of this difference in administration routes may be found in the feeding. Shortage on roughage for white veal calves reduces ruminal development to a well-functioning fermentative process, enabling oral administration of antimicrobials. The official Danish guidelines on antimicrobial treatment of cattle merely recommend oral administration of antimicrobials for gastrointestinal disorders of calves, such as *Escherichia coli* infections in preweaned calves. Caution against oral administration is based on limited absorption, as well as side effects for the intestinal flora (SEGES Dairy and Beef Research Centre et al., 2013). Additionally, oral administration of antimicrobials has been found associated with the development of antimicrobial resistance (Bos et al., 2012; Burow et al., 2014). Despite the allocation of oral antimicrobial treatments for gastrointestinal disorders, the majority of oral treatments were registered for respiratory disorders (Fig. 2).

Large variation was seen in antimicrobial usage between herd types (Fig. 3). As the majority of treatments is targeted respiratory disorders in the beginning of the fattening period (Pardon et al., 2012b), starter and full-line herds are expected to house the majority of diseased calves. In full-line herds, treatment of disease in the beginning of the production period is evened out by a longer time in the herd, which may explain the significantly lower use of antimicrobials compared to starter herds. Compared to Danish pig herds, Danish veal calf and young bull producing herds seem to use less antimicrobials. As shown in Fig. 3, the median standardized usage of antimicrobials (ADD_{200}/100 animals/day) was 2.14 in starter herds, 0.48 in finisher herds, 0.78 in full-line herds and 0.62 in herds with inconsistent movements. The median use of antimicrobials in Danish pig herds in 2012–2013 was around 8.0 for weaners, 0.8 for finishers and 1.8 for sows (Fertner et al., 2015). This higher usage in weaner pigs may be explained three main factors, Firstly, the indication of treatment differed, with gastrointestinal disorders being the primarily indication for treatment in pigs (Jensen et al., 2014), while respiratory disorders dominated in large veal calf and young bull producing herds. Secondly, pigs are categorized into more age-groups, which imply the standard weights for pigs being closer to the actual weight at treatment (15 kg (weaners), 50 kg (finishers) and 200 kg (sows/piglets)) compared to veal calves and young bulls (200 kg), where the applied standard weight is higher than the expected weight at treatment. Thirdly, the higher turn-over of pigs, where finishers are slaughtered at the average age of 5–6 months (Danish Agriculture and Food Council, 2014) may explain a higher usage.

One ADD_{200} may represent the treatment of one 200 kg calf or three 67 kg calves in one day. This means that when we use ADD_{200} for all veal calf and young bull producing herds, the estimated number of treatments in starter herds is likely to be underestimated, compared to the estimated number of treatments in finisher herds. We assumed that all registered drugs for a given age group on a given herd were actually consumed by that group of animals at the point in time where the drugs were purchased. This is most likely not the case. However, due to the long study period (one year) we expect irregularities in purchase patterns to be evened out to reflect an averagely actual usage.

The number of introduced calves and the number of suppliers were strongly correlated, which hindered the inclusion of both factors in the final risk factor analysis. Both factors are proxies for the risk of introducing pathogens and may impact the antimicrobial usage. Woolums et al. (2013) found the detection of respiratory disease in nursing beef calves to be positively associated with herd size. In addition, Taylor et al. (2010) and Cusack et al. (2003) reported commingling of cattle from various sources to increase the risk of respiratory disease, like Lava et al. (2016a) reported the purchase of veal calves to increase mortality, unwanted early slaughter and the application of metaphylaxis. Taylor et al. (2010) further reported purchase of calves from markets as a risk factor of respiratory disease. As demonstrated in our results, relatively few calves were sold on markets or through delivering traders in Denmark, which may explain, why we did not see an effect of these factors on the amounts of antimicrobial used. Due to the setup of the study as purely based on data from registers, it was not possible to study the effect of influencing factors in the management such as housing and shared air space.

Registration of purchased vaccines against BRSV, PI-3 and *Mannheimia haemolytica* serotype A1 was not found to influence the amount of antimicrobials. Due to the limited amount of herds using vaccines, we chose to dichotomize the variable in the risk factor analysis, as usage or not. A part of the insignificance may be explained by the limitations in our data. We only evaluated the effect on vaccination in the veal calf and young bull producing herd and not in the supplying dairy herd. Neither did we evaluate the administration procedure. An optimal vaccination program would require the supplying dairy herd manager to administer the vaccine 2–3 weeks prior to delivery in order to ensure sufficient immunoresponse at the time of arrival in the veal calf herd (Cusack et al., 2003). Another explanation of the insignificance may be found in the variety of pathogens. In Denmark, the most prevalent pathogens isolated from severe outbreaks of calf pneumonia in mono- or multi-culture include BRSV, *Pasteurella multocida*, *Histophilus somnus*, *Mannheimia haemolytica*, *Trueperella pyogenes* (Tegtmeier et al., 1999), Bovine coronavirus (Liu et al., 2006) and recently *M. bovis* (Nielsen, 2016), while PI-3 seems to play a minor role (Tegtmeier et al., 1999). Hence, a range of other pathogens may be involved in respiratory disorders than those three included in the vaccine. Cusack et al. (2003) did also not find any effect of vaccination on the prevalence of respiratory disorders and attribute the non-significance to the possibility of multiple pathogens being involved in the infection, making it infeasible to vaccinate against all.

Studies on antimicrobial treatment incidences in white veal calves in European countries have previously been carried out (Pardon et al., 2012a; Lava et al., 2016b). Treatment incidences in these two studies were not comparable to our results due to two issues: The lack of standardized standard dosages and the lack of standardized standard weights. Approved dosages of products with identical active substance and administration route have been found to differ almost four-fold between countries and up to ten-fold within the same country (Postma et al., 2015). Likewise, a consensus on approved standard weight is lacking. Previous publications have suggested or applied standard weights of 164 kg (Pardon et al., 2012a; Lava et al., 2016a,b), 140 kg (European Medicines Agency, 2015) and 172 kg (MARAN, 2016). Considering the large differences between white and rosé veal calves, it might be worthwhile to differentiate standard weights as done in the Netherlands (white (160 kg), rosé starter (77.5 kg) and rosé finisher (232.5 kg)) (Bos et al., 2013).

In VetStat, calves are defined as all bovines that have not calved. Hence, it is not possible to distinguish between heifers, young bulls and veal calves. We therefore excluded herds which seemed to produce heifers for dairy herds. Despite of the selection of large veal calf producers only, we still found quite some variation in production, e.g. herds producing both veal and young cattle. This may indicate a more heterogeneous Danish veal calf production compared to countries with a larger production of veal calves (Bos et al., 2012).

5. Conclusion

Based on register-data, we characterized the amount of used antimicrobials for large Danish herds producing veal calves and young bulls in 2014. Respiratory disorders followed by joints/limbs/CNS disorders were the diagnostic groups for which most antimicrobials were registered. The majority of antimicrobials were administered parenterally (85.6%), mainly with long-acting formulations.

For full-line herds we found the number of introduced calves to be positively associated with the amount of registered antimicrobials.

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4.5 Manuscript V

Weaner production with low antimicrobial usage: A descriptive study

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RESEARCH

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Weaner production with low antimicrobial usage: a descriptive study

Mette Fertner[1*], Anette Boklund[1], Nana Dupont[2], Claes Enøe[1], Helle Stege[2] and Nils Toft[1]

Abstract

Background: Health, productivity and antimicrobial use in the production of pigs are expected to be interrelated to some extent. Previous studies on register-based data have investigated these correlations with a subsequent large variation residing at the farm level. In order to study such farm factors in more detail we designed an elaborate interview-guide. By in-depth interviews of farmers with well-managed 7–30 kg (weaner) productions we sought to describe a set of common key-factors characterizing their management practices. Identification of such common practices could be used in follow-up projects, investigating whether identified factors really are characteristic for good-practicing famers.

Results: Eleven farms were selected for a farm visit and in-depth interview. Participating farms used less antimicrobials than the national median (8.2 animal daily doses/100 weaners/day), had a mortality below the national average (2.9%) and an average daily weight gain above the national average (443 g/day). Similarities were observed among participating farms, including the sectioning of farms, use of all-in-all-out procedures with subsequent cleaning, purchasing 7 kg weaners from only one source, as well as active participation in management by a committed farm owner. Most farmers had a specific point of focus in their management, and were convinced that this was the reason for their success. This included; feeding, treatment strategy, refurbishment of facilities and presence in the shed.

Conclusion: According to register data, participating farms were alike; in the good league regarding use of antimicrobials, mortality and daily growth. However, on-farm interviews elucidated more heterogeneity among farmers than expected. Most of the farmers had a specific point of focus, which they considered to be crucial for their good results. These results indicate the importance of non-registerable factors, highlighting the value of qualitative study techniques in the understanding of human actions. Further studies on the effect of various farmer types are recommended.

Keywords: Swine, pig, Antibiotic use, Management, Health

Background

Several databases with information regarding farm characteristics, infection status and antimicrobial use in pig farms are available in Denmark. Previous studies have investigated how much of the between-farm variation in antimicrobial use can be attributed to risk factors present in such registers. Variation at farm level has been found to constitute 38% [1] and 40% [2] of the total variation, underlining the importance that management, housing and the individual farmer have on the use of antimicrobials. Alternative study designs are therefore required to augment the value of register-based data.

Health, productivity and antimicrobial use at a farm are expected to be interrelated to some extent. Growth-enhancing effects of antimicrobials added to the feed in sub-therapeutic concentrations are well-known [3]. Furthermore, studies on the effect of phasing out growth promoters have shown an increased incidence of gastro-intestinal disorders among weaners in Denmark [4]. Sweden experienced an increased post-weaning mortality and decreased growth rate among weaners [5], which was not confirmed in Denmark [6].

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Antimicrobials prescribed for animals are reserved for therapeutic and metaphylactic purposes in the European Union [7]. A clear link can therefore be expected between the incidence of disease and amount of antimicrobials used. Additionally, it is recognized that a number of management-related parameters, as well as variation in treatment procedures can influence the use of antimicrobials in terms of disease-preventing initiatives. Procedures for disease prevention such as sectioning [8], hygiene [8] and handling of diseased pigs [9] have been negatively correlated with the use of antimicrobials. Due to its close link with gastrointestinal disorders [10, 11], feeding is also expected to have a significant influence on the use of antimicrobials in weaners. Treatment-related factors include the farmers' perception of metaphylaxis, the ability to identify clinically-diseased pigs, and compliance with veterinary recommendations for treatment.

Denmark produces more than 30 million fattening pigs per year and is one of the world's largest exporters of pork [12]. Among the European countries producing a similar amount of pork (Germany, Spain, France, Poland, Italy and the Netherlands) [12], Denmark has the lowest rate of antimicrobial use per animal [13]. Due to the large number of animals involved, pig production accounted for 76% of the veterinary antimicrobials prescribed in Denmark in 2012 [14] and it therefore receives the main political focus in terms of antimicrobial use. Calculated as animal daily doses (ADD) the majority of prescribed antimicrobials for pigs are administered for weaners (7–30 kg pigs), and mainly for gastrointestinal disorders [15, 16]. Since 2000, the amount of prescribed antimicrobials for all farms has been recorded in a Danish national database, VetStat [17]. However, parameters such as health, productivity and management practices for 7–30 kg pigs are not available in any national register. Average daily weight gain and mortality may be used as objective proxies for health and productivity, since diseased pigs are expected to have a reduced weight gain and may die [18]. Yet both these parameters are solely recorded on-farm, complicating the access of these data.

Our study examines well-managed farms: farms, which have overcome the apparent paradox of having a low rate antimicrobial use, simultaneously combined with low mortality and high productivity. It was our hypothesis that well-managed 7–30 kg (weaner) productions have a set of common key-factors characterizing their management practices. Using a semi-qualitative study design, we were able to obtain a detailed knowledge about the farms and their owners. This allowed us to further elucidate issues on which it is not possible to make inferences based on the information from national databases. The objective was to identify management-related factors which, according to the farmers' own perceptions, were the primary reasons for their positive results.

Methods

Participating farms were identified by the following selection procedure. Eleven veterinarians working in pig practice and representing different geographical regions and various veterinary practices, were contacted by telephone. Of these, seven agreed to participate in the study. They were encouraged to send a list of their clients with the lowest rates of antimicrobial use, and the highest rates of health and productivity. To fulfill the selection criteria, farms had to produce 7–30 kg pigs and not be organic or free-range. Each veterinarian selected three to eight of their affiliated pig farms, giving a total of 46 farms. The amount of prescribed antimicrobials for each of the farms was subsequently calculated, based on VetStat data. The national database VetStat receives information on prescribed antimicrobials from feed mills, veterinarians and pharmacies [15, 17]. Data reported by pharmacies (comprising more than 98% of all antimicrobials prescribed for pigs) for the period of January 1 to December 31, 2012, were included in this study. Antimicrobials were quantified as ADD [19, 20]. The number of ADD prescribed for weaners was aggregated for each farm and divided by the number of weaner days multiplied by 100. This standardized unit (ADD/100 weaners/day) approximates the daily percentage of weaners treated at the farm. Information on the number of weaners present in each farm was extracted from the Central Husbandry Register (CHR). The number of weaners at the farm was multiplied by 366 days (number of days in 2012) in order to compute the total number of weaner days.

Of the 46 farms initially selected, only those using less antimicrobials than the median of all Danish farms (8.2 ADD/100 weaners/day) were considered further. These 32 farms were contacted by telephone. If the farmers were interested in participating, they were required to forward their efficiency control. Efficiency control is a voluntary registration, which some farmers use to keep track of productivity. From the efficiency control, mortality and average daily weight gain were used as objective proxies for health and productivity at the farm. Only the farms with weaners with an average daily weight gain above the Danish average (443 g/day for weaners (7–30 kg)) and a mortality below the Danish average[a] (2.9%) were included in the study [21]. Farms with new infections were excluded, due to the risk of fluctuating management practices.

Eleven farms that fulfilled the inclusion criteria agreed to participate. These farms were visited and the person in charge of the production was interviewed by the corresponding author. Whenever possible, farm visits were carried out alongside the monthly veterinary advisory service visit. All visits were executed during February and March 2013. Each farm visit lasted between 2 and 4 h.

The interviews were structured in a semi open-ended manner, as described by Kvale and Brinkmann [22]. The structure of the interview was further discussed with an experienced interviewer. Due to the delicate topic of discussion, the decision was made not to record the conversations. The interview guide is available upon request. Typically, a farm visit started with a general assessment of the farm, conducted in association with the veterinarian. A thorough explorative interview was then conducted. Parameters expected to influence the antimicrobial use, health, and productivity at the farm including; employees, housing, management, hygiene, feed, biosecurity, movement of pigs and treatment procedures were addressed in the interview. Identification of these eight categories of questions were based on literature review prior to the study and subsequently presented to two specialized pig veterinarians to ensure inclusion of all important risk factors. Additionally, the farmer was asked what he/she considered the primary reasons for their successful production results. Five veterinarians were affiliated with these eleven farms and were interviewed separately. Veterinarians were first asked what they saw as the most important factors for a successful weaner production, and then they were asked to characterize their participating farms.

Results and discussion

The results presented in Table 1 represent factors which were mentioned by farmers and veterinarians as possible key-factors: SPF[b] infection status, management, internal biosecurity, pen hygiene between batches, feeding and treatment procedures.

In general, there was wide variation amongst farmers regarding their perception of which management parameters were the reasons for success in terms of low mortality, high daily weight gain and limited use of antimicrobials. They seemed to be divided into various categories with different points of focus, including feeding, presence in the shed, investment in facilities and treatment strategy. The choice of strategy seemed to be highly individual to each farmer. A committed farm owner, identified as a solid interest and participation in the management, characterized all participating farms. There were common factors among the interviewed farms, for example each received their 7 kg weaners from a single supplier, they implemented a high degree of sectioning, and a more or less consistent all-in-all-out production with cleaning between batches.

Farm demographics

All farms received 7 kg weaners from one single supplier; either their own or a regular sow farm. The weight at entrance varied from 6.5 kg to 8.5 kg. Some farmers prioritized heavy weaners at entrance (Farms 3 and 7). Nine of the participating farms participated in the voluntary SPF program, insuring that 7 kg weaners also originate from a SPF sow farm. The quality of 7 kg weaners, in terms of e.g. weight, health and growth potential is expected to be interrelated with the management at the sow farm. However, it was out of the scope for this project to go into further detail regarding management in the sow farm.

Three farms were free of all SPF-registered pathogens (Farms 4, 8 and 9), while other six SPF farms had a varying number of registered pathogens (Farms 2, 3, 5, 7, 10 and 11). Typically, the farms took into account their infection status in the management practices, in terms of sectioning and vaccine programs. SPF-registered pathogens were commonly screened, while surveillance of gastrointestinal disorders was uncommon [16].

Management

The estimated number of working hours per week varied from 1.7 to 9.3 per 1000 weaners. Farmer 8 considered presence in the shed to be crucial: *"If you want a successful weaner production, you need to spend sufficient hours in the shed"*. Despite having old buildings, this farmer had very good results in the weaner unit. In general, newer housing is expected to facilitate good practices (such as sectioning and hygiene), enabling fewer working hours without compromising results. However, "*what is crucial in the weaner production is to LOOK at the weaners, rather than at the calendar, to decide when it is time to sort them or change their feed*" (Farm 8). All farmers sorted the weaners to some extent, though the strategy varied. In general, farmers sorted by size, while a small number also sorted by sex. Sorting by sex enables differentiated feeding, which may increase the meat percentage and feed conversion, and may have some effect on the prevalence of tail biting [23].

In three of the farms (Farms 2, 5 and 8), the smallest weaners (<6 kg) were placed in a pen with fewer penmates and given a high quality feed mixture, and milk formula or sugar water was eventually added to increase the appetite. Under these conditions, initially small weaners had a higher growth rate and were therefore able to catch up with the larger weaners during the weaner period. The majority of farmers selling 30 kg pigs found it important to deliver a high quality product, since: "*Those 30 kg pigs entering that truck is my public image*" (Farm 3).

Table 1 Characteristics of 11 Danish weaner producing farms with low use of antimicrobials and high productivity

	1[a] (A and B[b])	2 (A and B)	3	4	5	6
Farm demographics						
Infection status	Unknown	+Myc[c]	+Ap(6 + 12), +Myc, +PRRS	Free of all SPF pathogens	+PRRS	Unknown
Biosecurity	Non-SPF	SPF	SPF	SPF, closed farm[d]	SPF, closed farm	Non-SPF
Number of 7–30 kg pigs	3,000 + 3,000	2,400 + 1,800	4000	1,250	2,000	1,800
Supplier	Regular sow farm	Own sow farm	Own sow farm	Own sow farm	Own sow farm	Regular sow farm
Housed days[e]	~140	~52	45	57	52	139
Weight (kg), entrance– exit	7–slaughter	6.5–32	8.5–28	6.6–33	7.6–30	7.8–slaughter
AM[f] usage (ADD_{15}/100/day)	4.16 and 7.19	3.9 and 5.7	2.7	7.37	6.03	0.6
Average daily weight gain (g/day)	800–825	~500	462	464	~500	705
Mortality (%)	~2	~2.5	1.5	1.2	0.7	1
Management						
Staff experience (years)	2	5	3	10 + (owner)	10+	10+ (owner)
Owner participating	With feeding	Daily	At delivery	Daily	No	Daily
Hours spent/week[g]	20 (3.3 h/1,000w)	7 (1.7 h/1,000w)	37 (9.3 h/1,000w)	11 (8.8 h/1000w)	15 (7.5 h/1000w)	NA
Sorting by	Size and sex	Size	Size and sex	Size	Size	Size and sex
Sorting frequency	Continuously	Twice	Twice	Twice	At entrance	Once
Internal biosecurity						
Sectioning	High	Not 100%[h]	High	High	High (for 80%)	Not 100%
Vaccinate weaners[i]	PCV2	PCV2	No	No	PCV2	NA
Pen hygiene between batches						
Beyond washing	Disinfection	–	Disinfection	–	–	Disinfection
Drying (days)	2	3–10	6	2–6	3–5	7 days
Incl. heat (days)	2	2–3	2	1	1–3	1–2
Feeding						
Type	Home-mixed wet + lactic acid bacteria	Home-mixed dry	Purchased pelleted	Home-mixed dry	Home-mixed wet	Home-mixed dry
No. of mixtures	3 (7–9 variations)	2+ extra	2	2	3 + extra	2
Zinc first 2 weeks	No	Yes	Yes	Yes	Yes	Yes
Treatments						
Primary indication	Unthrifty	Diarrhea at shift in feed	Diarrhea at shift in feed	Diarrhea 3 weeks after weaning	(Diarrhea for the 20% not-sectioned)	Unthrifty
Method	Injection or AM in feed in sick pen	Group (section)	Injection only	Group (pen)	Group (water in feed trough)	Injection
% treated per batch[j]	5%	50%	NA[k]	NA	20%	NA

	7	8	9	10	11
Farm demographics					
Infection status	+Myc	Free of all SPF pathogens	Free of all SPF pathogens	+Myc, +Ap6, +Ap12	+Myc, +PRRS
Biosecurity	SPF	SPF	SPF	SPF	SPF
Number of 7–30 kg pigs	2,200	4,000	4,000	3,300	1,720
Supplier	Own sow farm	Own sow farm	Own sow farm	Own sow farm	Regular sow farm
Housed days	44	50	56	55	55

Table 1 continued

	7	8	9	10	11
Weight (kg), entrance–exit	8.1–32	6.6–31.7	7.2–34.8	7.0–33.5	6.7–30.1
AM usage (ADD_{15}/100/day)	3.64	7.36	6.82	2.99	6.57
Average daily weight gain (g/day)	576	497	498	486	426[l]
Mortality (%)	1.6	0.8	1.4	1.7	1.6
Management					
Staff experience (years)	6	1	5+	1	10+ (owner)
Owner participating	Yes	Yes	Yes	Yes	Daily
Hours spent/week	7 (3.2 h/1,000w)	37 (9.3 h/1,000w)	NA	14 (4.2 h/1,000w)	10 (5.8 h/1,000w)
Sorting by	Size	Size	Size	Size	Size
Sorting frequency	Twice	Continuously	Once	Once	Once
Internal biosecurity					
Sectioning	High	Not 100%	Not 100%	High	Not 100%
Vaccine weaners	No	No	No	No	NA
Pen hygiene between batches					
Beyond washing	Disinfection	Disinfection	Disinfection	Disinfection	–
Drying (days)	13	4	7-10	1	2
Heating (days)	3	4	NA	1	2
Feeding					
Type	(1) Purchased pelleted (2) Homemixed wet	Purchased pelleted	Purchased pelleted	Purchased pelleted	Purchased pelleted
No. of mixtures	2	3+ extra	3	3	3
Zinc first 2 weeks	Yes	Yes	Yes	Yes	Yes
Treatments					
Primary indication	Diarrhea at shift in feed	Diarrhea at shift in feed	Diarrhea at shift in feed	Diarrhea 4–5 weeks after weaning	Diarrhea at shift in feed
Method	Group (half section)	Group (section)	Group (section)	Group (section)	Group (section)
% treated per batch	30–40%	100%	100%	100%	100%

The information presented in the table is obtained through registrations from VetStat, the farmers efficiency controls as well as semi-qualitative on-farm interviews.

[a] Farm No 1 and No 2 did not present their efficiency control, but reported estimated results on mortality and daily weight gain.

[b] A and B indicates that the farmer has two herds with 7–30 kg pigs.

[c] Presence of SPF pathogens, see endnote description.

[d] Closed SPF farms produce their gilts themselves and therefore do not receive pigs from other farms.

[e] The average number of days that a batch of weaners remains in a section.

[f] *AM* Antimicrobial.

[g] Labor hours spent per week is the number of weekly hours spent per 1,000 weaners, estimated by the farmer.

[h] "Not 100%" indicates defects in the sectioning procedures, such as: Weaners entering/leaving the housing having to pass through other sections, or pigs falling behind their batch mates being moved to another section.

[i] Informed by the herd owner, with the exception of farms 7, 8 and 9, where prescribed vaccines for weaners were obtained from VetStat.

[j] The percentage of pigs per batch being treated at least once during the weaner period, estimated by the farmer. Group treatment ("Group") was administered through the drinking water if nothing else is stated.

[k] Not available.

[l] Farm 11 was included, despite an average daily weight gain below 443 g/day, due to an entrance weight (6.7 kg) considerably lower than the national average (7.2 kg).

Internal biosecurity and pen hygiene between batches

All participating farms claimed to have an all-in-all-out production system. However, the extent to which this practice was managed differed between farms. Where sectioning was not practiced 100% efficiently, the design of the housing was typically regarded as a limiting factor.

For example, a shed previously used for cattle had been transformed into a pig shed (Farm 11) and in another farm, productivity exceeded the intended housing capacity (Farm 5). Farm 5 did not observe clinical diarrhea in the majority of weaners kept under strict sectioned conditions (80%). However, due to the inexpedient construction of the housing, 20% of the weaners were kept in a section with continuous production where diarrhea was observed and group treatment applied regularly. Sectioning [8] and improvement of housing facilities [24] has previously been found to influence the antimicrobial treatment frequency in pig farms. Additionally, a recent study by Laanen et al. [9] demonstrated that a high level of internal biosecurity (in terms of disease management) had a protective effect on the use of prophylactic group treatments, possibly due to a reduced transmission of pathogens within the farm.

In terms of hygiene between batches of pigs, it is recommended to wash, disinfect (for a minimum of 30 min), and subsequently leave pens empty for at least 2 weeks in order to reduce the transmission of *Lawsonia intracellularis* [25]. None of the participating farms were left idle for this time period, possibly due to the associated loss of income or lack of shed capacity. Nielsen et al. [8] found that the risk of antimicrobial group treatment in finisher farms increased by a factor of four, when the housing was never cleaned. Likewise, Laanen et al. [9], identified a positive correlation between cleaning and daily weight gain, possibly due to the reduction of gastrointestinal disorders.

Feeding

Good feeding practices may contribute to a healthy gastrointestinal microbiota, preventing diarrhea. More than half of the participating farms typically experienced diarrhea at shifts in feed (Farms 2, 3, 7, 8, 9 and 11), while only two farms did not observe diarrhea as the main clinical indication for treatment (Farms 1 and 6). Both mentioned the feeding as the reason: "*Diarrhea? No I adjust the feeding*" (Farmer 6). Whenever feces softened, they would decrease the grind of the feed slightly (Farm 6), or add a lactic acid bacteria starting culture (Farm 1). Farm 1 also added lactic acid bacteria starter culture in the feed for newly-arrived weaners. This is in accordance with prior scientific studies, demonstrating how probiotic bacteria, *Bifidobacterium lactis* Bb12 and *Lactobacillus rhamnosus*, may inhibit the adhesion of *Salmonella* sp., *Clostridium* sp. and *Eschericia coli* to the intestinal mucosa [26].

Treatment procedures

Farmers were asked to estimate the percentage of weaners treated in each batch, resulting in estimated treatment percentages ranging between 5 and 100%. Based on veterinary directions, the farmer chose when to initiate treatment, how to treat, the duration of treatment and what dose to use. All four parameters are highly dependent on the owner setting the standards of the farm, as well as the person in charge of the daily routines. The initiation of treatment depends on the ability to detect diseased animals, as well as the willingness of the farmer to tolerate the clinical signs. As the owner of Farm 3 stated: "*When you choose to have a low use of antimicrobials, you need to accept a certain level of diarrhea among your weaners*". This farmer rejected group treatment as "*It's a principle!*" In his experience, if the clinical diarrhea did not affect the general condition of the weaners they would recover without treatment. However, an "injection-only-strategy" has a considerable influence on the workload and subsequent labor costs, and can therefore be followed only by farms with the available resources. However, it can be argued that a high number of injections may stress the pigs and subsequently reduce welfare.

According to farmer No 3, the ability to detect diseased pigs and to initiate treatment at the optimal time is highly dependent on the person in charge of the daily routines. "*Some have the talent, while others will never learn*" (Farm 3). Hence, a person, which by the farmer may be characterized as talented, may use more antimicrobials in striving towards higher levels of health, welfare and productivity among the pigs. On the other hand, initiating early treatment may reduce transmission of disease and thus decrease the total amount of antimicrobials needed. However, some of the specialized pig veterinarians contacted during the initial study confirmed that farms with the highest level of health and productivity were not necessarily those using the lowest amount of antimicrobials.

More than half the participating farms administered antimicrobials in smaller units than on the section level (Farms 1, 3, 4, 5, 6, 7). One farm had two water pipes per section, enabling treatment of half a section at a time (Farm 7), while another had installed a medicine dispenser on each pen (Farm 4). Group treatment, where antimicrobials are administered through feed or water to a group of pigs, is widespread in pig production [27, 28]. Antimicrobials added to water are administered through a dispenser coupled to the water pipe. Hence, the configuration of the water pipes and/or dispenser types may have an impact on the number of treated animals at the farm, which may lead to a higher consumption of antimicrobials the larger unit each dispenser relates to.

Results from this study revealed some incongruence between recorded data and reality. In Farm 1 only 5% of the pigs received treatment. Despite this low treatment frequency, the apparent antimicrobial use as stated in VetStat was higher than expected (4.16 and 7.19), compared to farms treating 20% (6.03, Farm 5) and 50% (3.9 and 5.7, Farm 2) of their pigs. Pigs in Farm 1 stayed in the same section from a weight of 7 kg until slaughter. Antimicrobials were mainly being prescribed for weaners, but essentially administered after the pig had exceeded 30 kg of weight. This account was confirmed by the amount of antimicrobials being prescribed for finishers, which was close to zero. The treatment of a pig of 45 kg accounts for one ADD/100 finishers/day, but three ADD/100 weaners/day. This is based on the calculation of ADD, using 15 kg as a measure for a standard weaner and 50 kg as a measure for a standard finisher. As the antimicrobials were prescribed for weaners but used for finishers, the actual amount of ADDs for weaners at Farm 1 is expected to be markedly lower than stated in Table 1. Observations like this, elucidates the incongruence existing between VetStat data and use of antimicrobials in real life. Hence, in farms housing more age groups, it is essential for the veterinarian to be observant towards which age group of pigs actually is treated. When evaluating the antimicrobial use as ADD/100 pig/day, it is important to keep in mind that it is a statistical measure created to enable comparison of the relative consumption between farms, and is not necessarily a measure of the actual amount of antimicrobials used at the farm [19].

The impact on antimicrobial use of some of the factors discussed above, are supported by a currently unpublished study performed by Dupont et al., which investigates key factors which are related to a reduced use of antimicrobials. Dupont et al. found vaccination strategy and treatment method (smaller dosage, fewer group treatments, shorter treatment duration and changes in antimicrobial product) to be pointed out by farmers and veterinarians as the most important reasons for a decreased use of antimicrobials. Additionally, changes in feeding and increased compliance towards all-in-all-out procedures were mentioned.

Conclusions

According to register data, participating farms were alike; low use of antimicrobials, mortality and high daily growth. However, on-farm interviews elucidated more heterogeneity among farmers than expected. Most of the farmers had a specific point of focus which they considered to be crucial for their good results. Points of focus mentioned by the farmers included feeding, treatment strategy, refurbishment of facilities and presence in the shed. These results indicate the importance of studies going beyond register data. Qualitative study techniques are needed striving towards a better understanding of the actions taken behind data. Further studies on the effect of farmer types are recommended.

Endnotes

[a] Averages of daily weight gain and mortality are calculated as national averages of efficiency-control data from a representative sample of farms. The parameters are calculated as annual averages based on the number of inserted pigs.

[b] SPF, or Specific Pathogen Free farms, is a trademark of pig farms which ensures a certain level of external biosecurity through the restriction of entering visitors, equipment, feed and pigs. Hence, entering pigs need to come from another SPF farm with identical or higher health status [29]. Farms can be free from all (SPFX-) or some of the following: Porcine Reproductive- and Respiratory Syndrome (PRRS), *Actinobacillus pleuropneumoniae* (Ap), *Mycoplasma hyopneumoniae* (Myc), haemolytic *Serpulina hyodysenteriae* (Dys), toxin-producing *Pasteurella multocida* (Nys), *Haematopinus suis* and *Sarcoptes Scabiei* var. suis. If diagnosed with a disease, the abbreviation appertaining the pathogen is added as e.g. +Ap2 (presence of *Actinobacillus pleuropneumoniae*, serotype 2).

Author's contributions

MF designed the interview-guide, contacted participating farmers and veterinarians, carried out the on-farm interviews and drafted the manuscript under close supervision by NT and AB. ND participated in the design of the interview-guide, practicalities prior to farm visits an assisted in the data management. CE and HS participated in the design of the study. All authors have read and approved the final manuscript.

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Compliance with ethical guidelines

Competing interests

The authors declare that they have no competing interests.

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5. Discussion

All results in this thesis were based on the use of register data in Danish swine and veal calves. The results section presents the challenges and pitfalls to be aware of when working with and combining databases for pigs. It was shown that actual use of data highly influences data quality. Combination with other databases and the use of data for legislative and economic actions had an impact on the quality of data in the evaluated databases. Challenges related to the combination of data from two or more databases included issues such as incongruence between time scale and level of registration (e.g. animal- versus herd-level registrations) (Manuscript I).

The presented results show that pig herds with persistently high antimicrobial use throughout time tend to cluster in space. This was especially pronounced for sow farms, while there was more variation in the clusters of antimicrobial use for weaners, finishers and the combination of all three age groups. Clusters of high antimicrobial use coincided with areas of high farm density, and could be partially explained by production type, farm type and farm size (Manuscript II).

Furthermore, the results highlighted the impact of group-treatment procedures. Danish finisher farms which shifted from feed to water administration tended to increase their use of antimicrobials. This increase is most likely due to the treatment of a greater number of animals, as antimicrobials administered in feed (as top-dressing) are often administered at pen level, while antimicrobials administered in water are typically administered at section level (Manuscript III).

Results from the study of animal movements showed that the number of introduced calves was positively associated with on-farm antimicrobial use in herds producing veal calves and young bulls. However, the number of introduced calves is also highly correlated with the number of suppliers and herd size. It is therefore unclear whether the number of introduced calves or the number of suppliers has the greatest impact on antimicrobial use, yet both factors were proxies for the risk of introducing pathogens and therefore highlight the importance of external biosecurity (Manuscript IV).

Finally, the results of Manuscript V elucidate the divergence between data in the registers and on-farm observations. Included in this study were a number of weaner producers that seemed alike based on parameters present in the registers. Unexpectedly, they showed wide variation in their management procedures. Such results indicate the limitations of studies based solely on data from registers and highlight the importance of management factors and the influence of the farmer (Manuscript V).

5.1 Data availability

The overall aim of this thesis was to study associations between health, management and antimicrobial use in Danish swine and veal calves. Detailed antimicrobial purchase records were retrieved from VetStat and used as a proxy for the amount of antimicrobials used. However, finding a proxy for animal health was more challenging. We chose to focus on pigs, since they consume the majority of antimicrobials. For pigs, proxies for health and management could potentially be found in the database of laboratory submissions, SPF or meat inspection.

Around 50% of Danish pig farms submit samples to one of the two Danish diagnostic laboratories (DTU Vet, 2016). However, only SPF farms and farms using group medication submit samples regularly. This means that laboratory submissions may indicate the presence of pathogens rather than outbreaks of disease. It should also be noted that only a small number of antimicrobial prescriptions are a direct result of laboratory tests. In addition to this, only 14% of the mandatory laboratory tests relating to group treatments resulted in greater compliance with the recommendations, while the vast majority of herds retained their prior choice of antimicrobial product (Jensen et al., in prep). When working with laboratory submissions, it is important to note that the number of samples may be influenced by factors other than disease, for example the introduction of a new test or a change in prices. It was not possible to study the association between antimicrobial use and laboratory submissions in this thesis due to political issues.

SPF is a trademark indicating the health status of pigs at herd level. In 2015, 78% of all Danish sows and 35% of all Danish finishers were held in an SPF herd (SEGES, 2015). SPF farms are tested regularly for freedom of specific pathogens. Once a farm is categorized as positive, it is no longer tested for that particular pathogen. An SPF sow farm that is positive for PRRS may have the infection under control so that piglets are clinically negative, yet since they originate from a PRRS-positive farm, they are automatically categorized as positive (Kristensen et al., 2015). The treatment frequency in SPF farms was found to be three times higher than in non-SPF farms (Nielsen et al., 2002). However, in Manuscript II, SPF status did not have an effect on the multivariate clustering (p=0.519, Table 4). It should be noted that non-SPF farms do not necessarily have a higher infection pressure nor a lower level of biosecurity. These herds can purchase SPF animals and continue with the same regulations as SPF farms, but omit the SPF label for economic reasons. However, we did find a higher proportion of nucleus farms within the persistent clusters of antimicrobials (Manuscript II). One explanation could be that employees in nucleus farms have a lower threshold for initiating treatment, possibly caused by the higher value of animals. The effect of specific SPF pathogens was beyond the scope of this thesis, but has been evaluated by Kristensen et al. (2015), who found PRRS and *M. hyopneumoniae* to cause significantly higher antimicrobial use in weaners, while only a *M. hyopneumoniae*-positive status led to higher antimicrobial use in finishers.

Meat inspection data have the advantage of being recorded at animal level and may indicate prior clinical disease. However, meat inspection data have a low sensitivity, which additionally varies between abattoirs (Enoe et al., 2003) and indications (Bonde et al., 2010). Furthermore, meat inspection codes have changed over time, thus compromising longitudinal studies (Anonymous, 2009; Anonymous, 2010b). Three issues arise when combining VetStat data with meat inspection data. Firstly, there is a latency between antimicrobial treatment and the time of slaughter. This increases the need to quantify the antimicrobial use as an antimicrobial lifetime-exposure estimate (Andersen et al., submitted) to differentiate between antimicrobial exposure during the piglet, weaner and finisher phases. Secondly, meat inspection data are recorded at animal level, while VetStat is recorded at farm level. The prescription date and age group for which the drug was intended are recorded for each prescription in VetStat. The antimicrobial use for a given batch of pigs can be estimated from this information. However, evaluation of the causal pathway, between observations in VetStat and meat inspection, is complicated by the lack of individual antimicrobial registrations and the unknown point in time of clinical disease. New tools in the cattle industry may allow recordings of disease and treatment at the individual animal level, and enable the study of associations not currently possible using register data. Thirdly, meat inspection data mainly cover different diagnostic groups to those treated with antimicrobials. For weaners and finishers, antimicrobials are mainly administered for gastrointestinal disorders (Jensen et al., 2014). However, chronic enteritis is only found in <0.5% of slaughtered finishers (Alban et al., 2013), possibly because gastrointestinal disorders in the weaning period may have resolved at the time of slaughter. Among finishers slaughtered at a large Danish abattoir, 23% had a remark on respiratory disorders, while <0.5% had pericarditis, arthritis, osteomyelitis and tail lesions (Alban et al., 2013). Alban et al. (2013) and Dupont et al. (submitted) studied whether the introduction of the Yellow Card restrictive legislation on antimicrobial use affected the prevalence of slaughter remarks. They both found a lower prevalence of pneumonia (OR=0.7 and OR=0.6) following the introduction of the Yellow Card, possibly due to the positive effect of increased vaccination against PCV2 (+31%) and respiratory disorders (+21%) (Alban et al., 2013; DANMAP, 2015). Although vaccination is not seen as the most effective alternative to antimicrobial use, it is considered to be the most feasible one by experts on pig health from six European countries (Postma et al., 2015a).

Using data from registers requires thorough knowledge to identify the precautions and limitations of its application. Furthermore, it is questionable how well data in the registers are in agreement with the conditions on farms. Other studies have faced challenges linking on-farm observations with register data. In this respect, Knage-Rasmussen et al. (2015) did not find any association between on-farm observations of welfare and a generated animal welfare index based on data from meat inspection, antimicrobial use and mortality in Danish sow farms. A similar study in dairy herds by Otten et al. (2016) concluded that welfare assessments based on data from the registers may be used in the screening phase to give an indication of the level of welfare, yet it should not be used alone or to replace animal-based welfare assessments on farms. When compared to pigs, data on cattle may have the advantage of being collected in one single database and recorded at animal level.

5.2 Risk factors of antimicrobial use

Results presented in this thesis show a large variation between farms in the use of antimicrobials (Manuscript II and IV), which is in line with results from other countries (Sjolund et al., 2016). This variation may be partly explained by management-related factors, only some of which are represented in the registers. Risk factors present in the Danish registers include production type, farm size, veterinarians and geographical region (Hybschmann et al., 2011). Finisher farms have been found to have a higher antimicrobial use than integrated farms (Hybschmann et al., 2011; Van Der Fels-Klerx HJ et al., 2011), while small Danish pig farms tend to have a higher treatment incidence than medium or large farms, possibly due to better management and biosecurity in larger farms (Vieira et al., 2011; Hybschmann et al., 2011). In contrast, farm size was found to be positively associated with antimicrobial use in Dutch pig farms (Van Der Fels-Klerx HJ et al., 2011), which may be due to differences in management procedures. Hybschmann et al. (2011) found variation in antimicrobial use between geographical regions. Likewise, we identified a number of geographical clusters in which the use of antimicrobials was significantly higher (Manuscript II). Spatiotemporal surveillance of antimicrobial use patterns might be of use in the syndromic surveillance of disease outbreaks, but would require the quantification of antimicrobials using different techniques to those presented here, in order to deal with the time lag between registration and use. We hypothesized that veterinary affiliation might explain some of the persistent clustering. Hybschmann et al. (2011) and Vigre at al. (2010) found that 6%-11% of the total variation in antimicrobial use could be explained by factors relating to the veterinarian. Likewise, we aimed to study the effect of the veterinarian on antimicrobial clustering (Manuscript II), as well as on antimicrobial use in veal calves (Manuscript IV), yet this was not possible in either case.

The hierarchical structure of data, where the same veterinarian may practice in several herds, restricted our use of the veterinarian as a covariate in the cluster analysis (Manuscript II). Furthermore, several veterinarians may visit a single herd over time, causing cross-classification. This could be overcome by defining a "primary veterinarian" as the veterinarian prescribing most antimicrobials for each herd (Manuscript IV). For the 325 veal calf herds, we found 139 primary veterinarians. Only 15 (11%) were identified as primary veterinarian for more than four herds (5-12 herds), while 67 (48%) were primary veterinarian for one single herd (data not shown, Manuscript IV). This lack of hierarchical structure in the data prevented the inclusion of the veterinarian in the risk factor analysis (Manuscript IV).

Prior studies, based exclusively on register data, have found 38-40% of the total variation in antimicrobial use to reside at the herd-level (Vigre et al., 2010; Hybschmann et al., 2011). Therefore, management-related factors that are not represented in the registers seem to have a considerable impact on the use of antimicrobials. Risk factors that have been associated with high antimicrobial use in pig and veal farms include lack of quarantine, lack of sectioning, lack of clinical examination upon arrival (Lava et al., 2016b), low weaning age, vaccination against many pathogens, short farrowing rhythm, low internal and external levels of biosecurity (Laanen et al., 2013; Postma et al., 2016) and outbreak of diseases such as PMWS (Jensen et al., 2010). In addition, Dunlop et al. (1998a) found treatment practices in Canadian farrow-to-finish farms to be relatively consistent over time, which may be due to farmer habits or skills. Similarly, farmer habits may explain the positive correlation in antimicrobial use between different age groups of pigs, meaning that, for example, farms with high use in weaners also tend to have high use in finishers (Sjolund et al., 2016).

Our hypothesis that best-practice farmers have a set of similar management factors was not confirmed (Objective V). Instead, the results suggest that each farmer has their own focus of attention when it comes to management (Manuscript V). Studies on farmer and veterinary perceptions of antimicrobial use have increased in intensity in recent years (Gibbons et al., 2013; De Briyne et al., 2013; Coyne et al., 2014; Visschers et al., 2016). It has been acknowledged that sociological factors may influence the use of antimicrobials in veterinary medicine. Studies have indicated that some farmers have a demanding attitude over whether or not the veterinarian should prescribe antimicrobials, as well as the choice of drug (Gibbons et al., 2013; Coyne et al., 2014). This may increase the likelihood that some veterinarians will prescribe a drug (Gibbons et al., 2013), although veterinarians in general do not see this demand as an important factor affecting their prescribing behavior (De Briyne et al., 2013). To the best of the authors' knowledge, no such studies have been performed with Danish farmers, whose attitude might be influenced by the restrictive Danish legislation. It is clear, however, that farmers have very different approaches in terms of attitude and management (Manuscript V). Sociological studies have so far focused on farmers as a homogenous group (Coyne et al., 2014; Visschers et al., 2016), which emphasizes the need for further studies on what impact specific farmer types have on antimicrobial use.

Antimicrobial treatment of production animals in Denmark is restricted to therapeutic and metaphylactic treatments (Anonymous, 2014b). However, in practice, the border between metaphylactic and prophylactic treatment is a gray zone. The majority of treatments in veal and pig production are for gastrointestinal and respiratory disorders (Jensen et al., 2014) (Manuscript IV). It has been recommended that antimicrobial group medication (hence metaphylactic treatment) should be initiated when around 15% or more of the animals in a batch have diarrhea (Pedersen et al., 2014). However, diarrhea is not always of infectious origin. NSC is characterized as diarrhea in the absence of pathogens (Chase-Topping et al., 2007) and may explain the lack of association between the detection of pathogens and the level of diarrhea (Weber et al., 2015). NSC may be explained by diet (pelleted, wheat-based or diets with a high content of non-starch polysaccharides) and is commonly seen in relation to a change in feed (Chase-Topping et al., 2007; Pedersen et al., 2012). Likewise, several of the interviewed farmers in Manuscript V indicated diarrheal outbreaks occurred around the time of a change in feed. It has been suggested that outbreaks of diarrhea in pig farms where less than 15% of the pigs have an intestinal infection should be classified as low-pathogen diarrhea, and that group medication should not be used in such cases (Pedersen et al., 2014). Pedersen et al. (2015) found low-pathogen diarrhea in 7 of 38 farms and disproved the traditional perception that diarrheal outbreaks in weaners at the same farm have the same etiology over time. None of the farms were diagnosed with low-pathogen diarrhea in all three consecutive samples, highlighting an increased need for diagnostics and the potential to decrease the use of group treatments.

5.3 Methodology

When quantifying antimicrobials as ADD, it is important to keep in mind that ADD is a technical unit, with a number of related assumptions. The overall assumption is that all purchased antimicrobials are used. Studies on the relationship between the amounts of purchased and used antimicrobials are sparse, and it is inevitable that a certain amount of antimicrobials are wasted or remain in surplus. Furthermore, the ADD calculation includes assumptions about the applied dosage, weight at treatment and number of animals treated. Dosage has been shown to vary both within and between countries (Postma et al., 2015b). In Denmark, fundamental changes in the dosages were introduced in 2014 (Dupont et al., 2016). In this thesis, all ADD have been calculated based on the new DVFA dosages from 2014.

For calves, the estimated weight at treatment seemed to deviate from the actual weight at treatment (Manuscript IV). An explanation for this may be that only two age groups are used for cattle in VetStat, where the category “calves” covers all cattle that have not calved. The number of animals registered in the CHR was used in the calculations of ADD. Yearly extractions from the register were used (Manuscript II and III), and herds with changes in the number of registered pigs between the two data extractions were excluded because changes in herd size have a large impact on the calculated ADD. In order to achieve a more reliable estimation of the number of animals at risk, other studies have suggested using the number of pigs delivered for slaughter (Vieira et al., 2011) or registrations of pig movements (Birkegård et al., unpublished) as an alternative to using the herd sizes from the CHR. A limitation of the former is that it is restricted to slaughtered animals only, while pig movements and the CHR both are hampered by issues with data quality (Manuscript I).

Timeliness is an important issue when register data are used (Manuscript I). For prescriptions, registration is completed when the antimicrobial is purchased. However, in herds with a VAC, the veterinarian can prescribe antimicrobials for herd diagnoses for up to 63 days, which may cause a time lag between registration and use (Anonymous, 2015). Furthermore, when antimicrobials are prescribed for use over longer periods, the extraction of data over shorter time scales may lead to a risk of nil observations. Antimicrobial purchases in Manuscript III and IV were aggregated on a yearly scale, while antimicrobial purchases in Manuscript II were aggregated on a quarterly scale, increasing the number of nil observations. It is likely that these nil observations are not due to lack of antimicrobial treatment, but rather that they indicate the latency between date of purchase and date of use. To overcome the issue of nil observations, Vigre et al. (2010) suggested smoothing the amount of purchased antimicrobials over the time period until next purchase. This technique is likely to give a more appropriate estimate of the daily treatment incidence, where shorter time scales are to be studied.

In addition to the assumptions used in the standardization of ADD, it is also assumed that registrations of species, diagnostic group, veterinary ID, herd ID and age group are correct. Incorrect registrations of the latter two covered 1.3% of prescriptions for pigs in 2012-13 (Manuscript II). This percentage may be an underestimate, since antimicrobial recordings for pigs are expected to have fewer mistakes than other species due to the Yellow Card legislation. Veterinarians are able to prescribe antimicrobials for "farm diagnoses", while the drugs are recorded in VetStat for the diagnostic group that occurs most commonly (Laura Mie Jensen, personal communication). This may further complicate the evaluation of clinical disease based on VetStat, and reduce the registrations of antimicrobial treatments for less prevalent conditions. In addition, it should be kept in mind that some diagnostic groups are very diverse (e.g. "joint/limbs/CNS/skin" disorders) and are less suitable in the surveillance of certain diseases than more specific clinical diagnostic groups (e.g. "gastrointestinal" or "respiratory" disorders).

For this thesis, an overall qualitative comparison of various databases used in pigs was performed (Manuscript I). However, it would be of relevance to elucidate the extent to which VetStat and CHR data are able to estimate actual treatment frequencies, in order to quantify the divergence between actual and estimated use. Furthermore, it would be of interest to elucidate the extent to which recent political restrictions on antimicrobial use have affected data quality.

In some countries, actual use (Used Daily Doses, UDD) has been compared with estimated daily doses. In Belgium, the treatment incidence of Used Daily Doses (UDD) was estimated to be slightly lower than that of ADD, indicating that fewer pigs are treated in practice than theoretically estimated (Timmerman et al., 2006; Callens et al., 2012). However, Danish managers and veterinarians on farms that have reduced their antimicrobial use >10% following the implementation of the Yellow Card indicated their reduction could be attributed to the reduced length of treatments, reduced dosage of treatment, reduced use of group medication and increased use of vaccines (Dupont, submitted). Such initiatives are expected to lead to a higher number of treated pigs than estimated. The restrictive politics may explain why Danish farmers and veterinarians generally have a more reluctant attitude towards further antimicrobial reductions compared to their peers in other countries (Visschers et al., 2016). Under-dosing (in terms of a dosage that is too low), irregular treatment intervals or incomplete duration of treatment may lead to increased antimicrobial resistance (Catry et al., 2003), although the question of under- versus overdosing is hampered by the large differences in recommended doses of similar products both within and between European countries (Postma et al., 2015b).

The route of administration may also influence the level of resistance (Dunlop et al., 1998b; Varga et al., 2009; Burow et al., 2014). The majority of antimicrobials are administered orally for Belgian, French and German pigs (Sjolund et al., 2016) and for Danish weaners and finishers (Jensen et al., 2014). More specifically, it has been suspected that group treatment may be a risk factor in the development of Livestock Associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), which is found in 78% of Dutch veal calf herds (Bos et al., 2012) and 68% of Danish pig farms (DVFA, 2014). No Danish veal calf farm has yet been found to have persistent LA-MRSA infection (Hansen et al., unpublished). Whether this difference in resistance profiles can be attributed to variation in the route of administration remains unknown, as Danish veal calves are predominantly treated parenterally (Manuscript IV). It should be noted, however, that the route of administration is most often linked to dosing, where orally administered antimicrobials (administered as group treatments) are typically underdosed, while single-animal parenteral treatments most often are overdosed (Timmerman et al., 2006; Callens et al., 2012).

6. Conclusion and perspectives

This thesis demonstrated the usefulness and limitations of register data for research purposes. Inconsistencies in time scale and level of registration may complicate the combination of databases. This thesis did not fully succeed in studying the associations between health and antimicrobial use based on register data. However, we identified a number of factors in the registers that may influence the amount of antimicrobials used at herd-level, namely geographical region, treatment procedure and patterns of purchase.

This thesis had five objectives. Initially, we wanted to present the Danish pig registers and their pitfalls. Seven registers were described: CHR, Swine Movement Database, VetStat, diagnostic data from two laboratories (DTU-Vet and SEGES), SPF and the meat inspection database. In general, the validity of data generally improved when the data had an economic or judicial impact. Still, the extent to which register data represent reality has yet to be confirmed. This is of utmost importance due to the extensive use of data for research purposes and legislative actions.

A subsequent objective was to describe the distribution of antimicrobial use over time and space. A number of persistent geographical clusters in antimicrobial use were identified, hypothesized to be caused by affiliated veterinarian, manager factors and persistence of airborne pathogens. Hence, we found one persistent clusters in antimicrobial use for sows, two for finishers and none for weaners. A combined analysis of all tree age groups revealed three persistent clusters. Production type, farm type and farm size seemed to explain some of the persistent clustering in the multivariate cluster analysis, but the major reason for clustering remains to be analyzed.

Additionally, we wanted to study the effect of group-treatment procedures. It was demonstrated that pig herds changing group treatment from feed to water increased their antimicrobial use significantly. It cannot be excluded that changes in occurrence of clinical disease may have influenced the findings. Therefore, it would be relevant to follow up this type of study with further information on outbreak of disease and proportion of population treated. The overall shift in medication procedure might hypothetically have affected an overall increase in antimicrobial use, which remains for investigation.

Another objective was to study the effect of animal movements on the use of antimicrobials. This study was performed on full-line veal calf and young bull productions. Here, we found the number of introduced calves to be positively associated with the antimicrobial use, while no association was found on neither age at entrance nor time in the herd. What remains for investigation is to study whether these results are applicable in other veal calf production systems and the effect of management-factors unavailable in the registers.

Finally, we wanted to describe factors influencing antimicrobial use, which are not available in the registers. According to register data, participating farms were similar in terms of antimicrobial use, mortality and daily growth. On-farm interviews elucidated that most farmers had a specific point of focus, which they considered to be crucial for their good results. However, the points of focus varied between farmers and included feeding, treatment strategy, refurbishment of facilities and attentiveness in the shed. These results indicate the attitude of the farmer to be one of the main-drivers in appropriate use of antimicrobials, which suggest studying the effect of specific farmer-types.

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Because we humans are big and clever enough to produce and utilize antibiotics and disinfectants, it is easy to convince ourselves that we have banished bacteria to the fringes of existence. Don't you believe it. Bacteria may not build cities or have interesting social lives, but they will be here when the Sun explodes. This is their planet, and we are on it only because they allow us to be.

Bill Bryson

Associations between health, management and antimicrobial use in Danish swine and veal calves
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Ph.D. Thesis
July 2016

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